EU RISK MANAGEMENT PLAN FOR SUBUTEX®

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[a] Unless otherwise stated, the data in this document is up to 31 December 2017

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List of Abbreviations

Abbreviation	Term
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANSM	National Security Agency of Medicines and Health Products (French: Agence Nationale de Sécurité du Médicament et des Produits de Santé)
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under Concentration
BCP	buprenorphine-containing product(s)
CCDS	Company Core Data Sheet
CDC	Centers for Disease Control
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CTD	Common Technical Document
CYP	Cytochrome P450
DNA	Deoxyribonucleic Acid
DSM	Diagnostic and Statistical Manual
ECG	Electrocardiogram
EDD	Expected Date of Delivery
EEA	European Economic Area
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EPAR	European Public Assessment Report
ER	Emergency Room
EU	European Union
FAR	Final Assessment Report
HBV	Hepatitis B Virus
HCl	Hydrochloride
HCP	Healthcare Professional
HCV	Hepatitis C Virus
HDB	High Dose Buprenorphine (distinguishes between opioid dependence treatment doses [higher doses] and doses in the analgesic therapeutic dose range)
HIV	Human Immunodeficiency Virus
ICD	International Statistical Classification of Diseases and Related Health Problems
ICSR	Individual Case Safety Report
IDU	Injection Drug User
IM	Intramuscular
INDV	Indivior, Inc.
INN	International Nonproprietary Name
INR	International Normalised Ratio
IV	Intravenous
LBW	Low Birth Weight
LMP	Last Menstrual Period
LPD	Longitudinal Patient Databases
LSD	Lysergic Acid Diethylamide
MAH	Marketing Authorisation Holder
MOTHER	Maternal Opioid Treatment: Human Experimental Research
NAS	Neonatal Abstinence Syndrome

NICU	Neonatal Intensive Care Unit
NIDA	National Institute on Drug Abuse
NOWS	Neonatal Opioid Withdrawal Syndrome
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
OAMT	Opioid Agonist Maintenance Treatment
OUD	Opioid Use Disorder
PASS	Post-Authorisation Safety Study
PhV	Pharmacovigilance
PK	Pharmacokinetic(s)
PTD	Patient Treatment Days
PTY	Patient Treatment Years
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
RMS	Reference Member State
SC	Subcutaneous(ly)
SCARs	Severe Cutaneous Adverse Reactions
SmPC	Summary of Product Characteristics
TME	Targeted Medical Event
UK	United Kingdom
ULN	Upper Limit Normal
UNODC	United Nations Office on Drugs and Crime
USA	United States of America
WHO	World Health Organization

List of Tables

Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Buprenorphine
Pharmacotherapeutic group(s) (ATC Code)	Group: Other nervous-system drugs, drugs used in addictive disorders (N07BC01 - buprenorphine)
Marketing Authorisation Holder	Indivior (INDV) Europe Limited
Medicinal products to which this RMP refers	SUBUTEX® (buprenorphine sublingual tablets)
Invented name(s) in the European Economic Area (EEA)	SUBUTEX
Marketing authorisation procedure	Mutual Recognition Procedure Procedure number: FR/H/0147/001-003 France (RMS) + Concerned Member States
Brief description of the product	Chemical class: Buprenorphine is a white or off-white crystalline powder. Chemically, buprenorphine is 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4, 5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-6,14-ethanomorphinan-7-methanol, hydrochloride.
	Summary of mode of action: Buprenorphine is an opioid partial agonist at the μ (mu)-opioid receptor and an antagonist at the κ (kappa) opioid receptor. Buprenorphine's activity in opioid maintenance treatment is attributed to its slowly reversible link with the μ-opioid receptors in the brain, which reduces craving for opioids and opioid withdrawal symptoms. This assists in the attainment of treatment goals by minimising the need of opioid dependent patients to use illicit opioid drugs. Due to its opioid partial agonist activity, buprenorphine has a wide margin of safety, which limits its depressant effects, particularly on cardiac and respiratory functions.
	Important information about its composition: Buprenorphine hydrochloride equivalent to buprenorphine base: 0.4 mg, 2 mg, or 8 mg. The list of excipients includes: lactose, mannitol, maize starch, povidone K30, citric acid, sodium citrate, magnesium stearate.
Hyperlink to the Product Information	Refer to Module 1.3.1

Indication(s) in the EEA[b]	Current (if applicable): SUBUTEX is indicated for the treatment of opioid dependence, within a comprehensive therapeutic monitoring framework of medical social and psychological treatment.
	Proposed (if applicable): N/A
Dosage in the EEA[b]	Current (if applicable): *Initiation therapy (induction)* The recommended starting dose in adults and adolescents over 15 years of age is 2 to 4 mg as a single daily dose. An additional 2 to 4 mg may be administered on day one depending on the individual patient's requirement. During the initiation of treatment, daily supervision of dosing is recommended to ensure proper sublingual placement of the tablet and to observe patient response to treatment as a guide to effective dose titration according to clinical effect. *Dosage stabilisation and maintenance therapy* Following treatment induction, the patient should be rapidly stabilised on an adequate maintenance dose by titrating to clinical effect. Dose titration in increments or decrements of 2 to 8 mg of SUBUTEX to a level that holds the patient in treatment and suppresses opioid withdrawal effects is guided by reassessment of the clinical and psychological status of the patient. Clinical studies have shown that a maintenance dose of 12 mg to 16 mg of SUBUTEX used once daily is clinically effective for most patients. A maintenance dose of up to 24 mg used once daily may be needed, depending on the individual (a maximum single daily dose should not exceed of 24 mg buprenorphine). During maintenance therapy, it may be necessary to periodically restabilise the patient to a new maintenance dose in response to changing patient needs
	Proposed (if applicable): N/A
Pharmaceutical form(s) and strengths	Current (if applicable): SUBUTEX 8 mg sublingual tablets are uncoated oval white flat bevelled edged tablets, nominal dimensions 14 mm x 7 mm, embossed on one side with "B8". SUBUTEX 2 mg sublingual tablets are uncoated oval white flat bevelled edged tablets, nominal dimensions 10 mm x 5 mm, embossed on one side with "B2". SUBUTEX 0.4 mg sublingual tablets are uncoated oval white flat bevelled edged tablets, nominal dimensions 8 mm x 4 mm, embossed on one side with "04".

[b] This information is based on the current SUBUTEX CCDS and the French SUBUTEX SmPC

	The sublingual formulation is not designed to be split or broken.
	Proposed (if applicable): N/A
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety Specification

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Indication: Opioid Dependence

Incidence and Prevalence

Opioid dependence is characterised by a cluster of cognitive, behavioural and physiological features. The International Classification of Diseases, 10th edition (ICD-10) identifies six such features which include:

- a strong desire or sense of compulsion to take opioids
- difficulties in controlling opioid use
- a physiological withdrawal state
- tolerance
- progressive neglect of alternative pleasures or interests because of opioid use
- persisting with opioid use despite clear evidence of overtly harmful consequences

ICD-10 defines opioid dependence as the presence of three or more of the above features present simultaneously at any one time in the preceding year (WHO 2009).

As stated in the 2017 World Drug Report by United Nations Office on Drugs and Crime (UNODC), the number of past-year users of opioids and individuals who misused prescription opioids worldwide was estimated at 35.1 million people (range 28.3 to 42.7 million), of whom 17.7 million were estimated to have used opioids (heroin and opium) (UNODC 2017). In 2014, there were approximately 69 000 deaths from an opioid involved overdose worldwide (Knipper 2017).

According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) 2017 report, an estimated 1.4 million people received treatment for illicit drug use in the European Union (EU) during 2015 (1.6 million including Norway and Turkey). Opioid users represent the largest group undergoing specialised treatment and consume the greatest share of available treatment resources, mainly in the form of substitution treatment. Differences between countries can be very large, however, with opioid users accounting for more than 90% of treatment entrants in Estonia and less than 5% in Hungary. The latest data show that heroin use accounts for the majority, around 80%, of new opioid-related treatment demands in Europe. In addition, the overall decline in treatment demand related to heroin, observed since 2007, is no longer evident. Of particular concern is the increasing European estimate for drug overdose deaths, which has now risen for the third consecutive year; heroin is implicated in many of these deaths. Also in Europe, problems related to highly potent synthetic opioids appear to be growing, as indicated by increasing reports of non-fatal intoxications and deaths received by the Early Warning System (EMCDDA 2017).

While heroin still remains the most commonly used opioid in Europe, and opioid for the use of which most people seek treatment, there has been an increase in treatment demand related to prescription opioids (UNODC 2017). In 2015, 17 European countries reported that more

than 10 percent of all opioid treatment admissions were for problems related to opioids other than heroin. The most common opioids for the use of which treatment was sought were methadone, buprenorphine, fentanyl, codeine, morphine, tramadol and oxycodone. In some countries, non-heroin opioids represent the most common form of opioid use among treatment entrants (EMCDDA 2017).

Other countries also experiencing an increase in opioid use and opioid related harms include Canada with a death rate of opioid-related deaths of 8.8 per 100 000 population (Health Canada 2016), and Australia with an opioid related death rate of 0.78 to 1.19 deaths/100 000 population over 10 years (Blanch 2014). In the USA, from 2000 to 2013, the age-adjusted rate for overdose deaths involving heroin nearly quadrupled from 0.7 deaths per 100 000 in 2000 to 2.7 deaths per 100 000 in 2013 (Hedegaard 2015).

Demographics of the target population and risk factors for the disease

In the global burden of disease study, the prevalence of opioid dependence is higher among males than females, 0.30% and 0.14%, respectively (Degenhardt 2014).

Male opioid users were more likely to also use other illicit drugs; female opioid users were more likely to also abuse other prescription drugs (Wu 2010).

In 2015, the average prevalence of high-risk opioid use among adults (15–64) was estimated at 0.4% of the EU population, the equivalent of 1.3 million high-risk opioid users in Europe. Five countries account for three quarters (76%) of the estimated high-risk opioid users in the EU (Germany, Spain, France, Italy, United Kingdom [UK]). About 191 000 patients who entered specialised treatment in Europe reported opioids as their primary drug, 37 000 of whom were first-time entrants. Primary heroin users accounted for 79% of first-time primary opioid users entering treatment. Among heroin users in EU, the mean age at first use is 23 years, while the mean age at first treatment is 34 years. Among first-time patients entering drug treatment in 2015 with heroin as their primary drug, the male to female ratio was approximately 4:1 (EMCDDA 2017).

Risk factors for opioid dependence include: a personal history of substance abuse, family history of substance abuse, young age, a history of preadolescent sexual abuse, psychological stress, polysubstance abuse, poor social support, non-functional status caused by pain, exaggeration of pain, and unclear cause of pain (NIDA 2007).

It has been estimated that genetic factors account for between 40 and 60 percent of a person's vulnerability to addiction; this includes the effects of environmental factors on the function and expression of a person's genes. A person's stage of development and other medical conditions they may have are also factors. Adolescents and people with psychiatric illnesses are at greater risk of drug abuse and addiction than the general population (NIDA 2014).

Predictors of dependence on opioid medications among pain patients include substance abuse-related diagnoses, positive toxicology for opioids, and other medical diagnoses. Other patients at risk include those with idiopathic pain (no clear aetiology) or high levels of psychological distress or disability (Miller 2004).

The main existing treatment options

Psychosocially assisted treatment refers to the many ways in which professional and non-professional members of society can support the psychological health and the social environment of the opioid user, to help improve both the quality and duration of life. Assistance can range from the simple (e.g. provision of food and shelter) to the complex (e.g. structured psychotherapy) (WHO 2009).

The two, main pharmacological approaches to opioid dependence treatment are:

- Opioid Agonist Maintenance Treatment (OAMT) with long-acting opioids (methadone or buprenorphine (partial agonist)

- Pharmacological management of opioid withdrawal (WHO 2009).

Methadone and buprenorphine are effective evidence-based medications currently used in the treatment of opioid dependence and have been placed on the WHO model list of essential medicines (WHO 2009).

The primary aim of OAMT is to reduce the use of illicit opioids and manage abstinence by preventing withdrawal symptoms, reducing drug craving, and decreasing effects of additional opioids if they are consumed (UNODC-WHO 2017).

Methadone is the most common treatment in Europe (Segrec 2017). Methadone reduces the symptoms and signs of opioid withdrawal, reduces craving, and may mitigate euphoria (Dematteis 2017). In Europe, methadone is received by around two-thirds (63%) of substitution clients (EMCDDA 2017). A further 35% of clients are treated with buprenorphine-based medications, which also reduce the symptoms and signs of opioid withdrawal and reduce craving. Buprenorphine-containing products are the principal substitution drug in 8 countries (EMCDDA 2017). Other substances, such as slow-release morphine or diacetylmorphine (heroin), are more rarely prescribed, being received by an estimated 2% of substitution clients in Europe (EMCDDA 2017).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Long-term studies show that opioid dependence is a chronic relapsing illness. Estimates suggest a 2-5% annual remission rate, for example, 2 to 5% will stop using opioids in any one year (Lintzeris 2015).

The natural history of opioid dependence, if untreated, is morbidity and mortality. The main causes of death in this population are overdose and/or suicide, trauma, and infectious diseases (such as hepatitis C-related liver disease, human immunodeficiency virus (HIV) infection and endocarditis). Much of the overdose-related mortality associated with dependence on opioids is linked to use of other sedative drugs such as benzodiazepines and antidepressants and the use of alcohol which is a sedative as well. Effective treatment is associated with a 3-5-fold reduction in mortality (Lintzeris 2015).

Important co-morbidities

Hepatitis

People who inject drugs are at a risk for hepatitis B virus (HBV) and hepatitis C virus (HCV) infections through the sharing of needles and drug preparation equipment (CDC 2012). Current research shows that the prevalence of HCV is high among opioid dependent individuals. In fact, prior research showed that 80% of a sample of opioid dependent patients were positive for HCV antibody, and almost 67% were chronically infected (Murphy 2015). Chronic HCV infection can lead to long-term consequences including deaths and cases of severe liver disease, including cirrhosis and cancer, among an ageing population of high-risk drug users (EMCDDA 2017).

Across Europe, HCV is highly prevalent among injection drug users (IDUs). For every 100 people infected with HCV, 75-80 will develop chronic infection (EMCDDA 2017). A study was conducted in Spain which showed the incidence of HCV infection among IDUs was found to be 39.8/100 person-years and was 52.9/100 person-years among those who continued injecting during the follow-up period. Thus, the anti-HCV prevalence among the sample of injection drug users was close to the highest reported in the world (Vallejo 2015).

HIV/AIDS

Drug injection continues to play a role in the transmission of HIV. In 2007, it was estimated that there were 15.9 million IDUs worldwide, and 3 million of these IDUs were living with HIV (Grebely 2011).

In 2013, the average rate of newly reported HIV diagnoses associated with injection drug use was 2.5 per million population, and there were 769 notifications of new acquired immune deficiency syndrome (AIDS) cases in Europe attributable to injection drug use (EMCDDA 2015). In 2010, approximately 1 700 people died of HIV/AIDS attributable to injection drug use in Europe (EMCDDA 2015).

Psychiatric disorders

A high prevalence of psychiatric comorbidities, especially depressive, anxiety, and personality disorders, in opioid dependent patients, is well established (Roncero 2016).

A study to determine the prevalence of psychiatric disorders among young IDUs outside of a treatment setting found that major depression was the most prevalent disorder with an estimated lifetime rate of 25% (95% CI: 16.9-34.9) for men and 31% (95% CI: 21.2-42.1%) for women (Mackesy-Amiti 2012). A recent study showed a very high prevalence of psychiatric (comorbidities anxiety disorder, mood disorder, non-opioid substance use disorder, or personality disorder) among patients seeking treatment for co-occurring opioid use disorder (OUD) and chronic pain. Most participants in this study (81%) met the criteria for at least 1 psychiatric comorbidity, and the majority of participants (59%) met the criteria for at least 2 (Barry 2016).

Chronic pain

The use of opioid analgesics to treat chronic non-cancer pain, which is defined as pain lasting a least 3 months, has increased 3-fold since the early 1990s and has brought with it an

epidemic of nonmedical opioid use, opioid overdose, and OUD (Barry 2016). The intersection between pain management, opioid dependence, and addictive behaviour inflates the challenges of treating both opioid addiction and chronic pain (Dennis 2015). Measures that can be taken to prevent the abuse of prescription opioids in treating chronic pain include systems that encourage all opioid analgesia to be provided by one doctor, a graded approach to supervision of dosing, prescription of formulations less liable to abuse and careful patient selection (WHO 2009).

Part II: Module SII - Nonclinical Part of the Safety Specification

The animal pharmacology, pharmacokinetics (PK), and metabolic profiles of buprenorphine are well-established in the literature and through company-sponsored studies. The general pharmacology of buprenorphine relates to its actions as a μ-opioid receptor partial agonist and a κ -opioid receptor antagonist. It has high affinity for the μ-receptor an its long duration of action and lower level of physical dependence, compared to a full opioid agonist, relates to its prolonged and gradual dissociation from the μ-receptor. The μ-agonist action accounts for the effectiveness of buprenorphine as an analgesic and its effectiveness in the treatment of opioid dependence. Pharmacokinetic and metabolic profiles of buprenorphine in animals are similar to those in humans (Berson 2001). Buprenorphine has been extensively evaluated for safety in nonclinical toxicity studies; exhibiting a favourable safety profile. Buprenorphine was not teratogenic in rats or rabbits. At higher doses (systemic exposure > 2.4 times the human exposure at the maximum recommended dose of 24 mg buprenorphine, based on area under concentration [AUC]), buprenorphine was found to reduce reproductive capacity, embryofoetal survival and postnatal development. These findings seem likely related to parental behavioural effects and maternal toxicity indirectly affecting the foetus or offspring. The variety of routes and the wide range of doses employed in these studies precluded conclusive relationships, but it is considered that clinical use as prescribed poses no significant risk to reproduction or during pregnancy. Buprenorphine showed no genotoxic potential. The carcinogenicity study in mice with buprenorphine was negative, while the carcinogenicity study in rats found a trend toward increase in the incidence of testicular tumours that was not seen with mice. Overall, the nonclinical pharmacotoxicologic data for buprenorphine supports the efficacy and safety of SUBUTEX. A summary of key safety findings from the SUBUTEX nonclinical studies are provided in the table below. The exposure margins listed below are based on body surface area comparisons (mg/m^2) to the human sublingual dose of 16 mg buprenorphine via SUBUTEX.

Table 2: Key Findings from Nonclinical Studies

Key Safety findings (from nonclinical studies)	Relevance to human usage
Toxicity	
Single and repeat-dose toxicity • **Single-dose toxicity** Single-dose toxicity studies indicated that buprenorphine was of low acute toxicity. • **Repeat-dose toxicity** Repeated-dose toxicity studies showed a low order of toxicity, with pharmacotoxic signs generally related to the pharmacologic activity of the drug. Clinical signs generally included sedation, decreased activity, reduced food consumption and body weight gain. Aggressive behaviour, sensitivity to touch, restlessness and convulsion were occasionally seen in some animals. Studies ranging in duration from four weeks to one year, and employing oral, intravenous (IV),	Signs of toxicity include reduced body weight gain and food consumption, decreased activity, sedation or narcosis. The low order of acute oral toxicity largely mitigates the hazard with overdose of SUBUTEX. The data indicate that acute administration of buprenorphine is unlikely to present any significant risk to humans. Repeated-dose toxicology studies in rats and dogs utilising a variety of routes of administration indicate low general toxicity of buprenorphine. The data indicate that repeated-dose administration of buprenorphine unlikely to present any significant risk to humans.

Key Safety findings (from nonclinical studies)	Relevance to human usage
Toxicity	
intramuscular (IM) and subcutaneous (SC) routes of administration, suggest a virtual absence of systemic toxicity in the mouse, rat, dog, cynomolgus monkey, rhesus monkey, and baboon. A one-month sublingual study in monkeys found no significant adverse local effects, or local clinical, biochemical, or pathological findings. Chronic buprenorphine administration led to proliferation, fibrosis and hemosiderosis in the hepatobiliary system of dogs with oral dosing at 75 mg/kg/day for one year, with one mid-dose (3.5 mg/kg/day) possibly affected. Repeated-dose toxicology studies performed at maximum tolerated doses showed no evidence to suggest significant toxicity of buprenorphine in humans at dose significantly in excess of the clinical therapeutic dose level.	
Reproductive Findings	
• **Infertility Findings** Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily oral doses up to 80 mg/kg/day (estimated exposure was approximately 50 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) or up to 5 mg/kg/day IM or SC (estimated exposure was approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).	Because animal reproductive toxicity studies are not always predictive, the potential risk for humans is unknown.
No definitive drug-related teratogenic effects were observed in rats and rabbits at IM doses up to 30 mg/kg/day (estimated exposure approximately 20 times and 35 times, respectively, the human sublingual dose of 16 mg). Maternal toxicity resulting in mortality was noted in these studies in both rats and rabbits. Acephalus was observed in one rabbit foetus from the low-dose group and omphalocele was observed in two rabbit foetuses from the same litter in the mid-dose group; no findings were observed in foetuses from the high-dose group. Maternal toxicity was seen in the high-dose group but not at the lower doses where the findings were observed. Following oral administration of buprenorphine to rats, dose-related post-implantation losses, evidenced by increases in the numbers of early resorptions with consequent reductions in the numbers of foetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure approximately 6 times the human sublingual dose of 16 mg). In the rabbit, increased post-implantation losses occurred at an oral dose of 40 mg/kg/day. Following IM administration in the rat	No adequate and well controlled studies have been conducted with SUBUTEX in pregnant women that can be used to establish safety. Published data on human clinical experience with buprenorphine use during pregnancy suggest that a supervised therapeutic regimen is unlikely to pose a substantial teratogenic risk. Pregnant women involved in buprenorphine maintenance programmes are reported to have significantly improved prenatal care leading to improved neonatal outcomes when compared with women using illicit drugs. Because animal reproductive toxicity studies are not always predictive, the potential risk for humans is unknown. The use of buprenorphine during pregnancy should be assessed by the physician. Buprenorphine should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus.

Key Safety findings (from nonclinical studies)	Relevance to human usage
Toxicity	
and the rabbit, post-implantation losses, as evidenced by decreases in live foetuses and increases in resorptions, occurred at 30 mg/kg/day. Buprenorphine was not teratogenic in rats or rabbits after IM or SC doses up to 5 mg/kg/day (estimated exposure was approximately 3 and 6 times, respectively, the human sublingual dose of 16 mg), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the human sublingual dose of 16 mg), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95 times the human sublingual dose of 16 mg) and 25 mg/kg/day in rabbits (estimated exposure was approximately 30 times the human sublingual dose of 16 mg). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (estimated exposure was approximately 0.6 times the human sublingual dose of 16 mg) but were not observed at oral doses up to 160 mg/kg/day. Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (estimated exposure was approximately 6 times the human sublingual dose of 16 mg) in the absence of maternal toxicity or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the human sublingual dose of 16 mg) were not statistically significant. In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure approximately 0.3 times the human sublingual dose of 16 mg). No maternal toxicity was noted at doses causing post-implantation loss in this study.	
• **Peri-and Postnatal Development** No peri- or postnatal studies have been conducted with the SUBUTEX. Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine from Gestation Day 14 through Lactation Day 21 at 5 mg/kg/day (approximately 3 times the human sublingual dose of 16 mg). Studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the human sublingual dose of 16 mg), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the human sublingual dose of 16 mg), and after SC doses of 0.1 mg/kg/day	These results in rats correspond with reports of neonatal withdrawal in infants of women treated with buprenorphine during pregnancy. Because animal reproductive toxicity studies are not always predictive, the potential risk for humans is unknown. The use of buprenorphine during pregnancy should be assessed by the physician. Buprenorphine should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus.

Key Safety findings (from nonclinical studies)	Relevance to human usage
Toxicity	
and up (approximately 0.06 times the human sublingual dose of 16 mg). An apparent lack of milk production during these studies likely contributed to the decreased pup viability and lactation indices. Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the human sublingual dose of 16 mg).	
Kidney Toxicity	
In the 4-week intramuscular rat study, visual inspection of the mean relative organ weights suggested that kidney and adrenal weights increased in males and females receiving 90mg/kg/day (buprenorphine and naloxone [ratio 3:2]) (SUBOXONE Nonclinical Common Technical Document (CTD) 2002).	Renal impairment Renal elimination may be prolonged since 30% of the administered dose is eliminated by the renal route. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended when dosing patients with severe renal impairment (creatinine clearance <30 ml/min) (SUBUTEX CCDS 2016).
Liver Toxicity	
Buprenorphine undergoes hepatic first pass metabolism following oral administration via *O*-glucuronidation and cytochrome P450 (CYP) 3A (CYP3A)-mediated *N*-dealkylation into norbuprenorphine and cyclopropanecarboxaldehyde. The results of an *in vivo* study in mice suggested that the hepatotoxicity of buprenorphine is mainly due to its mitochondrial effects (SUBOXONE Nonclinical CTD 2002). Mitochondrial and metabolic activation of buprenorphine effects were investigated (SUBOXONE Nonclinical CTD 2002) in isolated rat liver mitochondria and microsomes, its toxicity in isolated rat hepatocytes and its *in vivo* toxicity in mice. Effects on liver were identified in studies in rats and dogs consistent with the results in other species.	Hepatic Impairment The active substance of SUBUTEX, buprenorphine, is extensively metabolised in the liver, and the plasma levels were found to be higher for buprenorphine in patients with moderate and severe hepatic impairment. Patients should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity or overdose caused by increased levels of buprenorphine. SUBUTEX sublingual tablets should be used with caution in patients with moderate to severe hepatic impairment (SUBUTEX CCDS 2016).
Carcinogenicity	
Two carcinogenicity studies with buprenorphine have been conducted with oral (dietary) administration in mice. It was concluded from these studies that buprenorphine is non-carcinogenic in mice at dietary doses up to 100 mg/kg/day, and when buprenorphine was administered to mice for 99 weeks at dosages of up to 2.0 mg/kg/day. Two (buprenorphine hydrochloride) carcinogenicity studies have been conducted in rats employing the oral (dietary) route of administration. In one study, statistically significant dose-related increases in	The clinical relevance of this finding is limited based on the estimated exposure. No increased risk of carcinogenicity is expected for buprenorphine as a result of SUBUTEX use.

Key Safety findings (from nonclinical studies)	Relevance to human usage
Toxicity	
testicular Leydig cell tumours in treated male groups were seen, according to the trend test adjusted for survival. Pairwise comparison of the high dose with control did not show statistical significance. No other significant tumourigenic or carcinogenic findings were seen. In the second study, no biologically significant changes seen in haematology, serum chemistry or urinalysis were considered biologically significant or treatment-related, though some variations occurred. Macroscopic findings were unremarkable. Some tissues in males showed dose-related increases in non-neoplastic lesions including unilateral and bilateral Leydig cell hyperplasia which was increased in all treated groups. With the exception of these Leydig cell lesions, none of the non-neoplastic lesions showed progression to neoplastic lesions.	
Genotoxicity	
Standard *in vitro* (Ames and cytotoxicity assay in human peripheral lymphocytes) and *in vivo* (rat micronucleus) genotoxicity tests with buprenorphine/naloxone (4:1) were negative, indicating that both compounds are devoid of genotoxic properties. Buprenorphine was studied in a broad series of tests utilising gene, chromosome, and deoxyribonucleic acid (DNA) interactions in both prokaryotic and eukaryotic systems. Results were negative in the majority of these assays but were equivocal in one (of several) Ames test and were positive in a few DNA synthesis assays using testicular cells from mice.	SUBUTEX is devoid of genotoxic properties.
Mechanisms for drug interactions	
Inhibition studies *in vitro* suggested that buprenorphine would not be expected to interact with drugs metabolised by CYP1A2, 2A6, 2B6, 2C9, 2C19 or 2E1. Since buprenorphine and many benzodiazepines are CYP3A substrates, the possibility of PK interaction was investigated. Buprenorphine was found to be a weak inhibitor of CYP3A *in vitro*; however, human PK studies indicated that co-administration of ketoconazole with SUBUTEX resulted in clinically significant increases in exposure to both buprenorphine and the metabolite norbuprenorphine, suggesting an increase in the bioavailability of buprenorphine. Available data indicate that co-administration of buprenorphine should not induce zidovudine toxicity; this is of importance since many injection drug users are HIV positive (SUBOXONE Nonclinical Summary Combined CTD 2002).	SUBUTEX should be used cautiously when co-administered with CYP3A4 inhibitors. An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased C_{max} and AUC of buprenorphine (approximately 50% and 70% respectively) and, to a lesser extent, of norbuprenorphine. Patients receiving SUBUTEX should be closely monitored and may require dose-reduction if combined with potent CYP3A4 inhibitors (e.g. protease inhibitors like ritonavir, nelfinavir or indinavir or azole antifungals such as ketoconazole, macrolide antibiotics or itraconazole). Concomitant use of CYP3A4 inducers with buprenorphine may decrease buprenorphine plasma concentrations, potentially resulting in sub-optimal treatment of opioid dependence with

Key Safety findings (from nonclinical studies)	Relevance to human usage
Toxicity	
	buprenorphine. It is recommended that patients receiving buprenorphine should be closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered. The dose of buprenorphine or the CYP3A4 inducer may need to be adjusted accordingly.
No nonclinical drug-drug interaction studies have been conducted with buprenorphine (SUBOXONE Nonclinical Summary Combined CTD 2002)**.** All indications suggest that there is no undesirable pharmacological interaction between buprenorphine and other agents such as naloxone and both drugs have a long history of safe use. For these reasons, classical safety pharmacology studies in animals have not been conducted with buprenorphine and this omission is considered to be fully justified. No pharmacodynamic drug interactions have been identified (SUBOXONE Nonclinical Summary Combined CTD 2002).	Based on the evidence from the nonclinical studies, human risk is likely to be minimal.
Other toxicity-related information or data	
Breast-feeding Buprenorphine and its metabolites are excreted in human breast milk. In rats, buprenorphine has been found to inhibit lactation.	The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUBUTEX and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

In conclusion, based on the results of the above nonclinical data accumulated over the course of the SUBUTEX clinical development programme, no additional nonclinical data appear to be needed.

Nonclinical pharmacotoxicologic profile of buprenorphine is well-established. The nonclinical pharmacology of buprenorphine supports the proposed therapeutic indication for treatment of opioid dependence and demonstrates good safety margins over non-targeted central nervous system (CNS), respiratory and cardiovascular effects. General toxicity studies establish a low toxicity potential for adverse effects at therapeutic exposure levels. The nonclinical information summarised are considered adequate to support the efficacy and safety of SUBUTEX sublingual tablets.

Part II: Module SIII - Clinical Trial Exposure

Estimates of cumulative subject exposure Table 4, based upon actual exposure data from 14 completed clinical trials, which are provided in Table 3. Further details on cumulative subject exposure categorised by dose, age, gender, and racial group are provided in Tables 5 through 7, respectively. Exposure data presented below is based on the 14 completed trials for which the MAH has datasets in an available format[c].

Table 3: Completed and Ongoing Clinical Trials with Exposure to SUBUTEX

Phase Count	Phase of Study	Protocol Number	Number of Subjects Enrolled	Number of Subjects Treated
Phase I: 7	Phase I	INDV-6200-101	27	27
	Phase I	RB-EU-14-0001	18	18
	Phase I	20-276-SA	48	48
	Phase I	20-277-SA	45	45
	Phase I	20-A78-AU	48	48
	Phase I	20-A79-AU	48	48
	Phase I	20-B17-AU	48	48
Phase II:3	Phase II	RB-UK-11-0018	26	26
	Phase II	RB-UK-11-0017	63	63
	Phase II A	RB-US-12-0005	124	124
Phase III:1	Phase III	CR96/013	106	101
Phase IV:3	Phase IV	P04843	241	241
	Phase IV	BU0902	79	76
	Phase IV	P05042	95	94
Total			**1 016**	**1 007**

Above numbers are pulled from clinical study reports and not from data sets

Table 4: Duration of Exposure – Completed Clinical Trial Exposure for SUBUTEX

Indication: Opioid Dependence			
Duration of exposure (at least)	**Persons**	**Patient treatment days (PTD)**	**Patient treatment years (PTY)**
1-30 days	425	5 450	14.92
31-90 days	3	106	0.29
Total	**428**	**5 556**	**15.21**

20-276-SA, 20-277-SA, 20-A78-AU, 20-A79-AU, 20-B17-AU, BU0902, CR96/013, RB-UK-11-0018, P05042 and RB-EU-14-0001 are not included in this table due to insufficient data.

[c] Data from completed trials as of 31-Dec-17. Race was not collected in study BU0902. Studies 20-276-SA, 20-277-SA, 20-A78-AU, 20-A79-AU, 20-B17-AU, BU0902, CR96/013, P04843, P05042, RB-UK-11-0017, RB-UK-11-0018, RB-US-12-0005 and RB-EU-14-0001 are complete.

Table 5: Cumulative Exposure to SUBUTEX by Dose

Indication: Opioid Dependence			
Duration of exposure (by dose)	**Persons**	**Patient treatment days (PTD)**	**Patient treatment years (PTY)**
2 mg	4	27	0.07
4 mg	161	629	1.72
6 mg	38	581	1.59
8 mg	180	1 800	4.93
10 mg	28	344	0.94
12 mg	95	609	1.67
14 mg	30	341	0.93
16 mg	84	747	2.05
18 mg	5	35	0.1
20 mg	35	114	0.31
22 mg	3	30	0.08
24 mg	38	386	1.06
Total	**701**	**5 643**	**15.45**

20-276-SA, 20-277-SA, 20-A78-AU, 20-A79-AU, 20-B17-AU, BU0902, CR96/013, RB-UK-11-0018, P05042 and RB-EU-14-0001 are not included in this table due to insufficient data. Subjects may be counted more than once as one subject can take more than one dose. For example, if one subject took 2 mg and 4 mg then that particular subject will be accounted in 2 mg as well as in 4 mg.

Table 6: Cumulative Exposure to SUBUTEX By Age Group and Gender

Indication: Opioid Dependence						
Age group (years of age)	**Persons**		**Patient treatment days (PTD)**		**Patient treatment years (PTY)**	
	M	F	M	F	M	F
< 25	46	22	579	291	1.59	0.8
25 - < 30	47	18	638	273	1.75	0.75
30 - < 35	69	21	743	239	2.03	0.65
35 - < 40	54	14	881	214	2.41	0.59
40 - < 45	49	8	560	94	1.53	0.26
45 - < 50	28	16	440	196	1.2	0.54
≥50	32	4	367	41	1	0.11
Total	**325**	**103**	**4 208**	**1 348**	**11.52**	**3.69**

20-276-SA, 20-277-SA, 20-A78-AU, 20-A79-AU, 20-B17-AU, BU0902, CR96/013, RB-UK-11-0018, P05042 and RB-EU-14-0001 are not included in this table due to insufficient data.

Table 7: Cumulative Exposure to SUBUTEX by Ethnic or Racial Origin

Indication: Opioid Dependence			
Ethnic/racial origin	**Persons**	**Patient treatment days (PTD)**	**Patient treatment years (PTY)**
American Indian or Alaskan Native	2	14	0.04
Asian	1	13	0.04
Black or African-American	37	450	1.23
White	145	1 408	3.85
Other	1	7	0.02

Indication: Opioid Dependence			
Ethnic/racial origin	**Persons**	**Patient treatment days (PTD)**	**Patient treatment years (PTY)**
Total	**186**	**1 893**	**5.18**

20-276-SA, 20-277-SA, 20-A78-AU, 20-A79-AU, 20-B17-AU, BU0902, CR96/013, RB-UK-11-0018, P05042 and RB-EU-14-0001 are not included in this table due to insufficient data. Race is missing for - 241 subjects in study P04843, 1 subject in study RB-US-12-0005

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Children/Adolescents Less Than 15 Years Old

Reason for exclusion: SUBUTEX may cause severe, possibly fatal, respiratory depression in children who accidentally ingest it. The CCDS for SUBUTEX warns to protect children against exposure and keep out of reach and sight of children. Use of SUBUTEX is contraindicated in children under 15 years (French SUBUTEX SmPC, June 2018).

Is it considered to be included as missing information? Yes

Geriatric Use (Elderly Patients Greater Than or Equal To 65 years old)

Reason for exclusion: The safety and efficacy of buprenorphine in elderly patients over 65 years of age have not been established.

Is it considered to be included as missing information? Yes

Pregnant or Breastfeeding Women

Reason for exclusion: Buprenorphine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Chronic use of SUBUTEX by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions) in the neonate.

Is it considered to be included as missing information? No; however, drug use during pregnancy and lactation is considered an identified risk.

Rationale: A post-authorisation safety study (PASS), PE-US001, was conducted to monitor pregnancy outcomes associated with exposure to SUBOXONE®, SUBUTEX and methadone among pregnant opioid dependent women using medical registries in Sweden and Denmark from 2005 to 2011 (PE-US001). In Sweden, in general, women exposed to SUBUTEX or methadone more often delivered preterm and C section were more common, when compared to the total population. There were 34 infants with neonatal abstinence syndrome (NAS) exposed to SUBUTEX. In Denmark, among the 571 823 mothers who gave birth during the study period, 564 exposed infants in 557 pregnancies were identified. Compared with the nonexposed, all recorded opioid use was associated with greater prevalence of preterm birth prevalence ratios were 3.5 (95% CI: 0.6<20.1) in SUBUTEX exposed and low birth weight

prevalence ratios 4.6 (95% CI: 0.8<26.7) in SUBUTEX exposed. No stillbirths occurred in SUBUTEX only exposed pregnancies.

A pregnancy assessment report was completed in 2013 that summarised all adverse event cases among women exposed to any buprenorphine product during pregnancy (SUBOXONE, SUBUTEX, TEMGESIC®, LEPETAN, BUPRENEX® or buprenorphine not otherwise specified) that were reported to INDV through 31 December 2012. A total of 7 268 individual case safety reports (ICSRs) from INDV's safety database, reported through 31 December 2012, were reviewed. The majority of these cases involved exposure to pregnancy without development of any adverse events. A total of 1 789 cases involved a pregnant woman/foetus or infant reported a targeted medical event (TME) of interest in pregnancy which were classified into the following categories: pregnancy loss; prematurity; other complications of pregnancy, labour/delivery and postpartum; congenital/foetal anomalies; NAS/neonatal drug withdrawal syndrome; other neonatal, infant and child conditions; developmental delay; and designated medical events.

A comprehensive review of the TME case safety data from all sources, including post marketing surveillance of pharmacovigilance (PhV) reports and the scientific literature, did not identify any new or emerging safety concerns in relation to the use of buprenorphine or buprenorphine-naloxone combination medicinal products during pregnancy.

Additionally, the Maternal Opioid Treatment: Human Experimental Research (MOTHER) study was a double-blind, double-dummy, flexible dosing, parallel-group randomised clinical trial of the relative maternal and neonatal safety and efficacy of buprenorphine monotherapy (SUBUTEX) versus methadone for the treatment of opioid dependence during pregnancy. The primary outcomes included the number of neonates requiring treatment for NAS, the peak NAS score, the total amount of morphine needed to treat NAS, the length of hospital stay for neonates, and neonatal head circumference among the two groups. The results showed that neonates exposed to buprenorphine *in utero* required significantly less morphine than did neonates exposed to methadone (mean total doses of 1.1 mg and 10.4 mg, respectively; $P < 0.0091$), and also had a significantly shorter hospital stay (10.0 vs. 17.5 days, respectively; $P < 0.0091$). The percentage of neonates requiring NAS treatment did not differ significantly between groups (P=0.26), nor did the groups differ significantly with respect to the peak NAS score (P=0.04) or head circumference (P=0.04) (Jones 2010).

Patients Who Have Been Shown to be Hypersensitive to SUBUTEX

Reason for exclusion: A history of hypersensitivity to buprenorphine is a contraindication to SUBUTEX use.

Is it considered to be included as missing information? No

Rationale: Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the postmarketing experience. Cases of bronchospasm, angio-oedema, and anaphylactic shock have been reported. The most common signs and symptoms include rashes, urticaria, and pruritus.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. However, given the extended postmarketing experience of the component products, for example, over 30 years for buprenorphine, the detection of signals for uncommon, rare or very rare adverse events would be less of a concern for SUBUTEX.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table 8: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Use in Children/Adolescents < 15 years old	Children were excluded from SUBUTEX clinical trial development programme.
Use in the Elderly (≥ 65 years old)	Elderly patients were excluded from SUBUTEX clinical trial development programme.
Pregnant women	Pregnant women were excluded from SUBUTEX clinical trial development programme. However, there were a total of 22 pregnancies reported during the SUBUTEX clinical development programme. The foetal outcome included the following: elective termination (N=2), full-term (N=9), pre-term birth (N=1), spontaneous abortion (N=1), and Unknown (N=9). In the PASS, PE-US001, in Sweden, 139 pregnant women were exposed to SUBUTEX. Of the 139 pregnant women, 34 infants had NAS. In Denmark, compared with nonexposed, all recorded opioid use was associated with greater prevalence of preterm birth prevalence ratios (3.5 (95%CI: 0.6<20.1) in SUBUTEX and low birth weight (LBW) prevalence ratio was 4.6 (95% CI: 0.8<26.7) in SUBUTEX. No stillbirths occurred in SUBUTEX only exposed pregnancies.
Breastfeeding women	Breastfeeding women were excluded from SUBUTEX clinical trial development programme.

<table>
<tr><th>Type of Special Population</th><th>Exposure</th></tr>
<tr><td>Patients with hepatic impairment</td><td>Patients with hepatic impairment were excluded from SUBUTEX clinical trial development programme.

For SUBUTEX clinical studies, patients were excluded who had aspartate aminotransferase (AST) levels ≥ 3 x upper limit of normal (ULN), alanine aminotransferase (ALT) levels ≥ 3 x ULN, or total bilirubin levels ≥ 1.5 x ULN.

However, in 2013, INDV completed a PASS (RB-US-08-0003) to determine PK of buprenorphine and naloxone in subjects with mild to severe hepatic impairment (child-Pugh Classes A, B and C), in HCV-seropositive subjects, and in healthy volunteers. Results indicated that SUBOXONE tablets were generally well tolerated in these groups of subjects with hepatic impairment, subjects with HCV infection, and healthy subjects. There were no safety concerns with regards to clinical laboratory parameters, vital signs, electrocardiograms (ECGs), or physical examinations. The overall results, based on the PK population excluding those subjects with emesis (related to $2xT_{max}$), showed that hepatic impairment or HCV infection resulted in statistically significant changes in exposure (C_{max} and AUC) to buprenorphine, norbuprenorphine, naloxone, or naloxone-3-β-D-glucuronide following a single sublingual dose of SUBOXONE tablet. In conclusion, the report concurred with the recommendation in the SmPC to consider dose adjustment for hepatically impaired patients.</td></tr>
<tr><td>Patients with renal impairment</td><td>Patients with renal impairment were excluded from SUBUTEX clinical trial development programme.</td></tr>
<tr><td>Patients with cardiovascular impairment</td><td>Patients with cardiovascular impairment were excluded from SUBUTEX clinical trial development programme.</td></tr>
<tr><td>Immunocompromised patients</td><td>Immunocompromised patients were excluded from SUBUTEX clinical trial development programme.</td></tr>
<tr><td>Patients with a disease severity different from inclusion criteria in clinical trials</td><td>Patients with a disease severity different from inclusion criteria in clinical trials were excluded from SUBUTEX clinical trial development programme.</td></tr>
<tr><td>Population with relevant different ethnic origin for SUBUTEX</td><td>Exposure to SUBUTEX by Ethnic Origin
<table><tr><th>Ethnic/Racial Origin</th><th>Number of Subjects</th></tr><tr><td>American Indian and Alaska Native</td><td>2</td></tr><tr><td>Asian</td><td>1</td></tr><tr><td>Black or African American</td><td>37</td></tr><tr><td>White</td><td>145</td></tr><tr><td>Other</td><td>1</td></tr><tr><td>Total</td><td>186</td></tr></table></td></tr>
<tr><td>Subpopulations carrying relevant genetic polymorphisms</td><td>Subpopulations carrying relevant genetic polymorphisms were excluded from SUBUTEX clinical trial development programme.</td></tr>
</table>

Part II: Module SV - Post-authorisation Experience

SV.1 Post-Authorisation Exposure for SUBUTEX

SV.1.1 Methods Used To Calculate Exposure

Marketing experience of buprenorphine in the form of SUBUTEX sublingual tablets has been determined by combining the numbers of dose units manufactured and released for sale by INDV to all countries other than the USA and the dose units sold in the USA by the US stock keeping unit.

To estimate patient exposure, unit sales for the time period were converted from number of tablets to the number of mg buprenorphine for each of the 0.4 mg, 2 mg and 8 mg tablet strengths. The number of mg for each tablet strength was summed to give the total number of mg which was then divided by the average daily dose to estimate the number of PTD. The total number of PTD was then divided by 365.25 to estimate the total number of PTY.

In most markets, the recommended starting dose is 2 to 4 mg; an additional 2 to 4 mg may be administered on Day 1 depending on the individual patients' requirements. Doses are increased until the desired clinical effect is reached for each patient, subject to a maximum daily dose of 24 mg. The rare requirement for a highly tolerant patient to receive a dose between 24 mg/d and 32 mg/d[d] should prompt a thorough review of the patient's progress toward meeting treatment goals. For the purposes of exposure estimation, it is assumed that the average daily dose is 8 mg (WHO 2017).

Cumulatively, worldwide patient exposure was estimated to be 5 640 029 PTY for SUBUTEX sublingual tablets, see Table 9 below.

Table 9: Exposure Table for Indication: Opioid Dependence

Region	Cumulative Patient Exposure to SUBUTEX from Marketing Experience Presented by Region		
	0.4 mg Tablet	2 mg Tablet	8 mg Tablet
Americas (mg)[e]			
Americas (PTD)			
Americas (PTY)			
Europe (mg)			
Europe (PTD)			
Europe (PTY)			

[d] The maximum daily dosage depends on the National approval and varies from 16 mg to 32 mg/day

[e] SUBUTEX is provided as unlicensed medicinal product in Canada and Qatar

Region	Cumulative Patient Exposure to SUBUTEX from Marketing Experience Presented by Region		
	0.4 mg Tablet	2 mg Tablet	8 mg Tablet
RoW (mg)[e]			
RoW (PTD)			
RoW (PTY)			
Global exposure (mg)			
Global exposure (PTD)			
Global exposure (PTY)			

PTD = Units Sold (mg buprenorphine) / 8, PTY = PTD / 365.25

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to diversion. As a partial agonist, buprenorphine abuse potential is less harmful than that of heroin, morphine or methadone. As a consequence, buprenorphine is commonly widely available for treatment of opioid dependence. The overdose risk of buprenorphine is increased with the abuse of buprenorphine and alcohol and other substances, especially benzodiazepines.

To minimise the risk of misuse, abuse and diversion, appropriate precautions should be taken when prescribing and dispensing SUBUTEX, such as to avoid prescribing multiple refills early in treatment, and to conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's level of stability.

INDV has undertaken a postmarketing study to determine effects of SUBOXONE overdose through a PASS (PE-US003). Retrospective safety evaluation studies were conducted to investigate the drug’s impact on total overdose death, in particular heroin-associated, and the relative contribution of buprenorphine to fatal overdose. Temporal trends in total drug-associated overdose deaths, as well as the proportion associated with buprenorphine, methadone, and heroin/morphine was examined. Further, the study investigated risk factors for fatal overdose associated with buprenorphine, in particular misuse by IV injection and concomitant intake of other CNS depressants. Trends in substitution treatment distribution, buprenorphine and methadone, were also assessed.

The results of PE-US003 for Sweden show that of the fatal cases related to buprenorphine 15% had a filled prescription with SUBUTEX or SUBOXONE, and 22% of the fatal methadone cases had filled prescription with methadone. The correlation between a fatal case related to buprenorphine and a filled prescription with SUBUTEX or SUBOXONE was hence relatively low. Presumably most of the subjects who died from a fatal overdose death by buprenorphine had obtained their drug illegally. In Denmark, approximately 200 fatal poisoning of drug abusers are registered each year. About 0.5% of these cases have been buprenorphine related. Recent figures from the EMCDDA recorded no buprenorphine-associated deaths in Denmark in their 2008-2011 reports. However, in Denmark, SUBUTEX and SUBOXONE are not reimbursed and are therefore not systematically recorded in the regional prescription databases. Hence, it was not possible to obtain data to divide buprenorphine-related deaths into SUBUTEX or SUBOXONE treatment. There were no indications of an increase in buprenorphine-related deaths in Denmark.

Part II: Module SVII - Identified and Potential Risks

Table 10: Identification of Safety Concerns in the Initial RMP Submission for SUBUTEX

Important identified risks	• Fatal overdose (including severe respiratory failure [mechanism for death by overdose]) • Respiratory depression/respiratory failure • Misuse and/or abuse (injection/intranasal) • Paediatric intoxication • Hepatitis, hepatic events, use in patients with hepatic impairment • Use during pregnancy, and lactation (effects on newborn and infant) • CNS depression
Important potential risks	• Medication errors when switching between SUBUTEX/SUBOXONE and new buprenorphine-containing products (BCP) which are not interchangeable with SUBUTEX/SUBOXONE
Missing information	• Use in children/adolescents < 15 years old • Use in elderly patients (≥ 65 years old)

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

The following risks are not considered important for SUBUTEX:

Use in patients with head injury and increased intracranial pressure is not considered an important risk as it is a well-known opioid class effect. Opioids may elevate cerebrospinal fluid pressure, which may cause seizures. Opioids should be used with caution in patients with head injury, intracranial lesions, other circumstances where cerebrospinal pressure may be increased, or history of seizure.

Peripheral oedema is not considered an important risk. Peripheral oedema is considered a commonly reported adverse drug reaction during postmarketing surveillance. Additionally, peripheral oedema is considered a common treatment-related undesirable effect in clinical studies of SUBUTEX.

Drug dependence is not considered an important risk. The risk of drug dependence with use of opioids is well-known to healthcare professionals (HCP) and does not require additional PhV activities or additional risk minimisation measures. Buprenorphine is a partial agonist at the μ-opioid receptor and chronic administration may produces dependence of the opioid type. Drug dependence is listed as the most commonly reported adverse drug reactions during postmarketing surveillance. Appropriate precautions should be taken when prescribing and dispensing SUBUTEX, such as to avoid prescribing multiple refills early in treatment, and to

conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's level of stability.

Drug withdrawal syndrome is not considered an important risk. The risk of drug withdrawal syndrome with use of opioids is well-known to HCPs and does not require additional PhV activities or additional risk minimisation measures. Adverse drug reactions related to withdrawal symptoms (e.g., insomnia, headache, nausea, hyperhidrosis) are commonly reported during postmarketing surveillance. In patients with marked drug dependence, initial administration of buprenorphine can produce withdrawal effect similar to that associated with naloxone. Prior to treatment initiation with SUBUTEX, consideration should be given by the prescriber to the type of opioid dependence (e.g., long- or short-acting opioid), the time since last opioid use and the degree of opioid dependence. To avoid precipitating withdrawal, induction with buprenorphine should be undertaken when objective and clear signs of withdrawal are evident. Abrupt discontinuation of buprenorphine treatment is not recommended as it may result in a withdrawal syndrome that may be delayed in onset.

Allergic reaction(s) is not considered an important risk. The risk of allergic reactions with use of opioids is well-known to HCPs and does not require additional PhV activities or additional risk minimisation measures. As stated in the product information, cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the postmarketing experience. The most common signs and symptoms include rashes, urticaria, and pruritus. Cases of bronchospasm, angioedema, angioneurotic oedema and anaphylactic shock have been reported. SUBUTEX is contraindicated in patients with hypersensitivity to buprenorphine or to any other component of the product.

Switching between SUBUTEX and SUBOXONE is not considered an important risk. Switching from SUBUTEX to SUBOXONE with equivalent dose of buprenorphine does not raise significant clinical concerns, although dose adjustments may be necessary in some cases, especially in the later phase of the treatment (Cassoux 2002). A PASS study (PE-US004) was conducted that included monitoring patients switching from SUBOXONE to buprenorphine. The study concluded that none of the safety terms specially searched for and classified as adverse event/reaction reached the 5% threshold. Based on existing clinical studies, significant clinical concerns related to this transfer are not anticipated. When used sublingually, SUBOXONE and SUBUTEX have similar clinical effects and are interchangeable; however, when switching between SUBOXONE and SUBUTEX, the prescriber, patient and treatment staff should agree to the change, and the patient should be monitored in case a need to readjust the dose occurs. In June 2018, the product information for SUBUTEX was updated to harmonise SUBUTEX posology with SUBOXONE with regard to the same maximum daily dose of both buprenorphine induction dose (i.e., 2 to 8 mg) and maintenance dose (i.e., 24 mg).

Reason for Not Including an Identified or Potential risk in the List of Safety Concerns in the RMP:

The following known risks require no further characterisation and are followed up via routine PhV through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers:

- use in patients with head injury and increase in intracranial pressure

- peripheral oedema
- drug dependence
- drug withdrawal syndrome
- allergic reaction(s)
- switching between SUBUTEX and SUBOXONE

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk 1: Fatal overdose (including severe respiratory failure [mechanism for death by overdose])

Risk-benefit impact: A potential outcome of overdose is suppression of respiratory function and death. A number of cases of death due to respiratory depression have been reported, particularly when SUBUTEX was used in combination with benzodiazepines, when high dose buprenorphine (HDB) was administered to non-opioid dependent individuals who had not developed a tolerance to the effects of opioids, or when buprenorphine was otherwise not used according to prescribing information. Deaths have also been reported in association with concomitant administration of buprenorphine and other CNS depressants

From the overdose study (PE-US003), recent figures at the EMCDDA recorded no buprenorphine-associated deaths in Denmark in their 2008-2011 reports. In Sweden, in the fatal cases related to buprenorphine 15% had a filled prescription with SUBUTEX or Suboxone, 22% of the fatal methadone cases had filled prescription with methadone. The correlation between a fatal case related to buprenorphine and a filled prescription with SUBUTEX and Suboxone was hence relatively low and most of the subjects who died from a fatal overdose death by buprenorphine had obviously obtained the drug illegally.

Thus, fatal overdose is classified as an important identified risk.

Important Identified Risk 2: Respiratory depression/respiratory failure

Risk-benefit impact: A number of cases of deaths due to respiratory depression have been reported, particularly when SUBUTEX was used in combination with benzodiazepines, when HDB was administered to non-opioid dependent individuals who had not developed a tolerance to the effects of opioids, or when SUBUTEX was otherwise not used according to prescribing information. Deaths have also been reported in association with concomitant administration of buprenorphine and other CNS depressants such as alcohol, other opioids, tranquilisers (including benzodiazepines), sedatives or hypnotics. SUBUTEX may cause severe, possibly fatal, respiratory depression in children who accidentally ingest it. Protect children against exposure.

Thus, respiratory depression/respiratory failure is classified as an important identified risk.

Important Identified Risk 3: Misuse and/or abuse (injection/intranasal)

Risk-benefit impact: SUBUTEX can be misused or abused in a manner similar to other opioids, legal or illicit. Some risks of misuse and abuse include overdose, spread of blood borne viral infections, respiratory depression and hepatic injury. SUBUTEX misuse by someone other than the intended patient poses the additional risk of new drug dependent individuals using buprenorphine as the primary drug of abuse and may occur if the medicine is distributed for illicit use directly by the intended patient or if the medicine is not safeguarded against theft. Additionally, IV misuse of buprenorphine has been documented and usually occurs when heroin or the opioid of choice is either not readily available, is of poor quality, or there is no control on prescribing.

In cases of drug abuse or intentional drug misuse, some adverse experiences attributed to the act of misuse rather than the medicinal product itself have included: local reactions (such as cellulitis or abscess that are sometimes septic), potentially serious acute hepatitis, pneumonia, endocarditis and other serious infections.

To minimise the risk of misuse, abuse and diversion, appropriate precautions should be taken when prescribing and dispensing SUBUTEX, such as avoid prescribing multiple refills early in treatment, and to conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's level of stability.

Thus, misuse and/or abuse (injection/intranasal) is classified as an important identified risk.

Important Identified Risk 4: Paediatric intoxication

Risk-benefit impact: SUBUTEX may cause severe, possibly fatal, respiratory depression in children who accidentally ingest it. SUBUTEX is only available in child-proof blister packs, and the CCDS for SUBUTEX warns to protect children against exposure and to keep out of reach and sight of children.

Use of SUBUTEX is contraindicated in children under 15 years (French SUBUTEX SmPC, June 2018).

Thus, paediatric intoxication is classified as an important identified risk.

Important Identified Risk 5: Hepatitis, Hepatic Events, Use in Patients with Hepatic Impairment

Risk-benefit impact: Cases of acute hepatic injury have been reported in opioid dependent patients, both in clinical trials and in postmarketing adverse reaction reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of cytolytic hepatitis, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. In many cases, the presence of pre-existing mitochondrial impairment (genetic disease, liver enzyme abnormalities, viral infection such as hepatitis B and chronic hepatitis C, alcohol abuse, anorexia, concomitant use of other potentially hepatotoxic medicines, or ongoing drug use by injection) may have a causative or contributory role.

Patients who are positive for viral hepatitis, on concomitant medicinal products and/or have existing liver dysfunction are at greater risk of liver injury, and these underlying factors must be taken into consideration before prescribing SUBUTEX and during treatment.

The effects of hepatic impairment on the PK of buprenorphine were evaluated in a postmarketing study. Buprenorphine is extensively metabolised in the liver, and plasma levels were found to be higher for buprenorphine in patients with moderate and severe hepatic impairment. Patients should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. SUBUTEX should be used with caution in patients with moderate to severe hepatic impairment.

Thus, hepatitis, hepatic events, use in patients with hepatic impairment is classified as an important identified risk.

Important Identified Risk 6: Use during pregnancy and lactation (effects on newborn and infant)

Risk-benefit impact: Buprenorphine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Chronic use of SUBUTEX by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions) in the neonate. The syndrome is generally delayed for several hours to several days after birth.

Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates.

Neonatal drug withdrawal syndrome has been reported among newborns of women who have received buprenorphine products during pregnancy. The syndrome may be milder and more protracted than that from short acting full μ-opioid agonists. The nature of the syndrome may vary depending upon the mother's drug use history.

Thus, use during pregnancy and lactation (effects on newborn and infant) is classified as an important identified risk.

Important Identified Risk 7: CNS depression

Risk-benefit impact: SUBUTEX may cause drowsiness, particularly when used together with alcohol or CNS depressants (such as benzodiazepines, tranquilisers, sedatives or hypnotics). Deaths have also been reported in association with concomitant administration of buprenorphine and other CNS depressants.

SUBUTEX has moderate influence on the ability to drive and use machines when administered to opioid dependent patients. SUBUTEX may cause drowsiness, dizziness, or impaired thinking, especially during treatment induction and dose adjustment. If used with alcohol or central nervous system depressants the effect is likely to be more pronounced. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities.

Thus, CNS depression is classified as an important identified risk.

Important Potential Risk 1: Medication errors when switching between SUBUTEX/SUBOXONE and new buprenorphine-containing products (BCP) which are not interchangeable with SUBUTEX/SUBOXONE

Risk-benefit impact: The switching between buprenorphine-containing products which are not interchangeable may be necessary (e.g., if a person moves between care settings from the community in to prison or between prisons and doesn't need restabilisation). In addition, the risk for inadvertent substitution (prescribing and dispensing errors) may occur in the event of HCPs not being aware that some BCPs, for example, Espranor/Orobupre (further referenced as Espranor) and Zubsolv, are not interchangeable with SUBUTEX/SUBOXONE or their generics.

Espranor and Zubsolv have different bioavailability compared to SUBUTEX and SUBOXONE. Therefore, the dose in mg can differ between products. Once the appropriate dose has been identified for a patient with a certain product (brand), the product cannot readily be exchanged with another product.

Espranor (buprenorphine oral lyophilisate) bioavailability is 25-30% higher than SUBUTEX (Espranor Public Assessment Report, July 2015). The recommended starting dose of Espranor is 2 mg – 6 mg compared to 2 mg – 8 mg for other oral buprenorphine preparations and the maximum single daily dose for Espranor is 18 mg not 24 mg as with SUBUTEX (Espranor SmPC, July 2017 ; French SUBUTEX SmPC, June 2018).

Zubsolv is a rapidly disintegrating sublingual tablet containing 0.7 mg / 1.4 mg / 2.9 mg / 5.7 mg / 8.6 mg / 11.4 mg buprenorphine (as hydrochloride) and 0.18 mg / 0.36 mg / 0.71 mg / 1.4 mg / 2.1 mg / 2.9 mg naloxone (as hydrochloride dihydrate) as active substances. The differences between SUBOXONE and Zubsolv formulations imply that switching between the two *(at the same dose in mg)* would not reproduce the same plasma concentrations of buprenorphine (Zubsolv: EPAR, January 2018). In comparative bioavailability studies, Zubsolv 11.4 mg/2.9 mg displayed equivalent buprenorphine exposure to 16 mg/4 mg (2 x 8 mg/2 mg) buprenorphine/naloxone administered as conventional sublingual tablets; however, Zubsolv 2 x 1.4 mg/0.36 mg displayed 20% lower buprenorphine exposure to 2 x 2 mg/0.5 mg buprenorphine/naloxone administered as conventional sublingual tablets (Zubsolv SmPC, March 2018). A lower buprenorphine exposure from Zubsolv may potentially result in reduced opioid receptor stimulation leading to withdrawal symptoms when switching from another buprenorphine product at a dose level below 5.7 mg/1.4 mg. In addition, owing to the long terminal half-life of buprenorphine, it would take several days to reach a new steady state when switching between formulations (Zubsolv: EPAR, January 2018).

Thus, medication errors when switching between SUBUTEX/SUBOXONE and new BCPs which are not interchangeable with SUBUTEX/SUBOXONE is classified as an important potential risk.

Missing Information 1: Use in Children/Adolescents Less Than 15 Years Old

Risk-benefit impact: SUBUTEX may cause severe, possibly fatal, respiratory depression in children who accidentally ingest it. SUBUTEX is only available in child-proof blister packs, and the CCDS for SUBUTEX states to protect children against exposure and to keep out of reach and sight of children. Use of SUBUTEX is contraindicated in children under 15 years (French SUBUTEX SmPC, June 2018).

Thus, the use of SUBUTEX in children/adolescents < 15 years old is classified as missing information.

Missing Information 2: Use in Elderly Patients (Greater Than or Equal To 65 Years Old)

Risk-benefit impact: The safety and efficacy of buprenorphine in elderly patients over 65 years of age have not been established. Opioids should be administered with caution to elderly or debilitated patients.

Thus, the use of SUBUTEX in elderly patients ≥ 65 years old is classified as missing information.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information[f]

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Fatal Overdose (including severe respiratory failure [mechanism for death by overdose])	
Potential mechanisms	Respiratory depression is the leading mechanism of death in fatal overdose. Suppression of respiratory function is a dose-dependent property of opioids. Alcohol and benzodiazepines interact with buprenorphine (Jones 2004). Severe alcohol intoxication, alcohol withdrawal syndrome, and *delirium tremens* are associated with risk of respiratory depression. Concomitant use of alcohol and buprenorphine increase risk of respiratory depression.
Evidence source(s) and strength of evidence	Section 4.4 of the SUBUTEX CCDS states that a number of cases of death due to respiratory depression have been reported, particularly when SUBUTEX was used in combination with benzodiazepines, when high dose buprenorphine was administered to non-opioid dependent individuals who had not developed a tolerance to the effects of opioids, or when buprenorphine was otherwise not used according to prescribing information. Deaths have also been reported in association with concomitant administration of buprenorphine and other CNS depressants. Section 4.5 of the SUBUTEX CCDS states that a combination with benzodiazepines may result in death due to respiratory depression of central origin; which could lead to respiratory arrest and death. From the overdose study (PE-US003), recent figures at the EMCDDA recorded no buprenorphine-associated deaths in Denmark in their 2008-2011 reports. In Sweden, the fatal cases related to buprenorphine 15% had a filled prescription with SUBUTEX or SUBOXONE, 22% of the fatal methadone cases had filled prescription with methadone. The correlation between a fatal case related to buprenorphine and a filled prescription with SUBUTEX and SUBOXONE was hence relatively low and most of the subjects who died from a fatal overdose death by buprenorphine had obviously obtained the drug illegally.

[f] MedDRA version 21.0 was used to classify events. MedDRA up versioning may sometimes recode and reclassify events.

Characterisation of risks	To date, 1 271 events classified as "Fatal events" were reported with SUBUTEX (reporting rate 22.5 events per 100 000 patient years). Of these, 305 events were classified as fatal overdose. The majority of these events (n=154) involved Toxicity to various agents. Of the 1 271 events cumulatively received for SUBUTEX, 767 of the events (in 331 cases) involved concomitant use of CNS depressants.
Risk factors and risk groups	Patients abusing buprenorphine, especially IV abusers, polysubstance abusers, combining the use of buprenorphine with alcohol, benzodiazepines, and other drugs, are at high risk for overdose and associated respiratory depression. In substance-abuse treatment, SUBUTEX should be used with caution in patients with compromised respiratory function (e.g. chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis). Severe alcohol intoxication, alcohol withdrawal syndrome, and *delirium tremens* are associated with the risk of respiratory depression.
Preventability	Supervised substance-abuse treatment on risk of death from SUBUTEX overdose is a major tool preventing overdose in SUBUTEX abusers. To minimise the risk of misuse, abuse and diversion, appropriate precautions should be taken when prescribing and dispensing buprenorphine, such as to avoid prescribing multiple refills early in treatment, and to conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's level of stability. Buprenorphine should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis). Patients with the physical and/or pharmacological risk factors above should be monitored, and dose reduction may be considered.
Impact on the risk-benefit balance of the product	With the risk minimisation measures in place for the risk of fatal overdose, it is expected that the impact on the risk-benefit balance of SUBUTEX is low.
Public health impact	Fatal overdose among opioid abusers is a known public health problem and generally, opioid abuse hinders work and life productivity and its management/acute treatment adds strain to healthcare resource budgets. Prescriber, patient, caregiver education is a useful tool to increase community awareness of the risk of fatal overdose.

Important Identified Risk: Respiratory Depression/Respiratory Failure	
Potential mechanisms	Respiratory depression is the leading mechanism of death in fatal overdose. Suppression of respiratory function is a dose-dependent property of opioids. Alcohol and benzodiazepines interact with buprenorphine (Jones 2004). Severe alcohol intoxication, alcohol withdrawal syndrome, and *delirium tremens* are associated with the risk of respiratory depression. Concomitant use of alcohol and buprenorphine increases the risk of respiratory depression.

	The mechanisms of developing respiratory depression from opioid use are self-potentiating in that hypoventilation impairs gas exchange, resulting in increased carbon dioxide (hypercapnia) and decreased oxygen (hypoxia) and pH (respiratory acidosis). In turn, suppression of the chemoreceptor responses to increased carbon dioxide levels blunt the normally protective central response which would increase breathing efforts. This "vicious cycle" may result in profoundly low oxygen (hypoxemia) and/or respiratory arrest (Jungquist 2011). Buprenorphine may cause drowsiness, particularly when used together with alcohol or CNS depressants such as benzodiazepines, tranquilisers, sedatives or hypnotics. One of the most serious problems with opioids is that overdose can give rise to respiratory depression, coma, and death. Buprenorphine in combination with benzodiazepines or other CNS depressants (including alcohol), has been associated with significant respiratory depression and death.
Evidence source(s) and strength of evidence	Section 4.4 of the SUBUTEX CCDS states that a number of cases of death due to respiratory depression have been reported, particularly when SUBUTEX was used in combination with benzodiazepines, when high dose buprenorphine was administered to opioid non-dependent individuals who had not developed tolerance to the effects of opioids, or when buprenorphine was otherwise not used according to prescribing information. Section 4.5 of the SUBUTEX CCDS states that a combination with benzodiazepines may result in death due to respiratory depression of central origin; which could lead to respiratory arrest and death. A case of respiratory arrest occurred during a clinical study (CR96/005) in which the patient severely overdosed on heroin and oxazepam that lead to the event of respiratory arrest. This case was considered possibly related to SUBUTEX.
Characterisation of risks	To date 267 events classified as “Respiratory Depression/Respiratory Failure” were reported with SUBUTEX (reporting rate 4.7 events per 100 000 patient years). Of these, 241 were serious and 70 events involved a fatal outcome. Of the 267 events cumulatively received for SUBUTEX, 159 of the events (in 147 cases) involved concomitant use of CNS depressants.
Risk factors and risk groups	The risk for CNS depression is increased in patients who are on prescription medications for anxiety/depression and those with habitual alcohol intake. Risk factors for developing respiratory failure includes smoking tobacco products, excessive alcohol intake, a family history of respiratory disease or conditions, injury to the spine, brain, or chest, and immunocompromised patients (Macon 2017). Other risk factors include concomitant use of CNS depressants and respiratory illness.
Preventability	SUBUTEX should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis). SUBUTEX should not be used together with alcoholic drinks and must be used cautiously with medicines containing alcohol.

	Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking SUBUTEX and should also be cautioned to use benzodiazepines concurrently with SUBUTEX only as prescribed.
Impact on the risk-benefit balance of the product	With the risk minimisation measures in place for the risk of respiratory depression/impairment, it is expected that the impact on the risk-benefit balance is low.
Public health impact	Respiratory depression due to overdose among opioid abusers is a known public health problem and its management/acute treatment adds strain to healthcare resource budgets. Prescriber, patient, caregiver education is a useful tool to increase community awareness of the risk of respiratory depression/failure.

Important Identified Risk: Misuse and/or Abuse (injection/intranasal)	
Potential mechanisms	Buprenorphine can be misused or abused in a manner similar to other opioids, legal or illicit. The most common pattern of abuse involves crushing the sublingual tablets and injecting the resulting extract (Cicero 2005).
Evidence source(s) and strength of evidence	Opioids are the most commonly abused type of prescription drug and appear to be the largest contributor of increases in the prevalence of prescription drug abuse in the USA (McHugh 2015). Buprenorphine has been associated with life-threatening respiratory depression and death. Many, but not all, postmarketing reports regarding coma and death involved misuse by self-injection by the IV route or were associated with the concomitant use of buprenorphine and benzodiazepines or other CNS depressants, including alcohol. In cases of IV misuse, local reactions, systemic viral (HIV, HCV and HBV), microbial (endocarditis) [Cooper 2007, Chong 2009, Lee 2009], and fungal (*Candida endophthalmitis*) [Hirsbein 2008, Cazorla 2005, Aboltins 2005, Aguilar 1979, Cassoux 2002] infections, and sometimes septic reactions have been reported. Many of the histories provided from postmarketing data in France indicated that some or all of the drugs detected at post-mortem had probably been injected. The majority of the non-fatal cases of misuse, which came to medical attention (n=72) also included histories of injection misuse. Buprenorphine is relatively well absorbed by a nasal route (Lindhardt 2000), and intranasal buprenorphine abuse has been reported (Simojoki 2008). The most frequently reported postmarketing adverse event observed with buprenorphine sublingual tablets was drug misuse or abuse.
Characterisation of risks	To date, 14 164 events classified as “Misuse/Abuse (intravenous/intranasal)” were reported with SUBUTEX (reporting rate 251.2 events per 100 000 patient years).

	The complications of SUBUTEX IV and intranasal misuse and abuse are typical for IV and intranasal abuse in general. To date, 1 555 of the 14 164 reported AEs characterised as misuse/abuse were considered to be serious. A total of 387 events had a fatal outcome.
Risk factors and risk groups	Risk factors associated with opioid abusers include 18-25-year olds, the male gender, patients with psychiatric disorders (including depression and bipolar disorder), exposure to violence and sexual abuse, a patient with a history of substance abuse, and a family history of substance abuse (Brady 2016). Opioid and polysubstance abusers are at risk of IV and intranasal abuse of SUBUTEX. Sub-optimal treatment with SUBUTEX may prompt medication misuse by the patient, leading to overdose or treatment dropout.
Preventability	To minimise the risk of misuse, abuse and diversion, appropriate precautions should be taken when prescribing and dispensing SUBUTEX, such as to avoid prescribing multiple refills early in treatment, and to conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's level of stability. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking SUBUTEX and should also be cautioned to use benzodiazepines concurrently with SUBUTEX only as prescribed. Patient's Brochure for use of BCP, July 2017 (distributed by pharmaceuticals companies marketing BCP, under the authority of the ANSM) alerts the patients that injection or sniffing of buprenorphine is dangerous for their health, 'If you inject or sniff, you are at risk of overdose (respiratory failure), infections, liver damage and vascular lesions (injection), or nasal mucosal damage (sniff). The injection or the sniff do not allow to reach a stabilisation of good quality, necessary condition for your wellbeing'.
Impact on the risk-benefit balance of the product	With the risk minimisation measures in place for the risk of misuse/abuse, it is expected that the impact on the risk-benefit balance of SUBUTEX is low.
Public health impact	Opioid abuse is a major public health concern and is associated with a high level of morbidity and mortality in Europe (EMCDDA 2017). Since the prevalence of opioid abuse and misuse has increased globally, leading to an increase in deaths from overdose and individuals seeking treatment for opioid use disorders, a number of policy and educational initiatives have been implemented to help providers and patients, prescribe and use opioids more responsibly (Brady 2016). These include increasing access to effective treatments and harm reduction strategies including education, monitoring opioid cost and supply, strategic reimbursement for clinicians, and targeted research funding (Hawk 2015). Risks of infection and death due to respiratory depression constitute known public health problems posed by IV opioid abuse. Although IV SUBUTEX abuse is reported, benefits of therapeutic SUBUTEX use substantially outweigh risk.

Important Identified Risk: Paediatric intoxication	
Potential mechanisms	Suppression of respiratory function is a dose-dependent property of opioids. Respiratory depression is the leading mechanism of death in fatal overdose.
Evidence source(s) and strength of evidence	A retrospective study reported 86 cases of buprenorphine overdose in children; 54 developed toxicity (UNECE 2007). Children who ingested >2 mg buprenorphine were more likely to experience a clinical effect; all who ingested >4 mg experienced some effect. In 54 children who developed toxicity, the clinical effects included drowsiness or lethargy (55%), miosis (21%), vomiting (21%), respiratory depression (7%), agitation or irritability (5%), pallor (3%), and coma (2%). No fatality was reported.
Characterisation of risks	To date, there have been 597 events classified as 'paediatric intoxication' in SUBUTEX (reporting rate 10.6 events per 100 000 patient years). Of these, 382 events were serious, and 74 events had a fatal outcome. From the overdose study (PE-US003), recent figures at the EMCDDA recorded no buprenorphine-associated deaths in Denmark in their 2008-2011 reports. In Sweden, the fatal cases related to buprenorphine 15% had a filled prescription with SUBUTEX or SUBOXONE, 22% of the fatal methadone cases had filled prescription with methadone. The correlation between a fatal case related to buprenorphine and a filled prescription with SUBUTEX and SUBOXONE was hence relatively low and most of the subjects who died from a fatal overdose death by buprenorphine had obviously obtained the drug illegally. Respiratory depression may occur as a result of CNS depression. It may lead to respiratory arrest and death.
Risk factors and risk groups	Paediatric patients exposed to buprenorphine are likely to have a household member who is using buprenorphine and, in most cases, may be inadvertently (accidentally) exposed to it. Children who are exposed will exhibit signs and symptoms of opioid toxicity, including respiratory depression, altered mental status, miosis within 8 hours of reported exposure (Toce 2017). In older paediatric patients who may be opioid abusers and abusing buprenorphine, especially IV abusers, polysubstance abusers, combining the use of buprenorphine with alcohol, benzodiazepines, and other drugs, are at high risk for overdose and associated respiratory depression. In substance-abuse treatment, SUBUTEX should be used with caution in patients with compromised respiratory function (e.g. chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis).
Preventability	SUBUTEX is only available in child-proof blister packs and the labelling clearly instructs to keep out of reach and sight of children. Buprenorphine may cause severe, possibly fatal, respiratory depression in children who accidentally ingest it. Use of SUBUTEX is contraindicated in children under 15 years (French SUBUTEX SmPC, June 2018).
Impact on the risk-benefit balance of the product	With the risk minimisation measures in place for the risk of paediatric intoxication, it is expected that the impact on the benefit-risk balance of SUBUTEX remains positive.

Public health impact	Fatal overdose due to paediatric intoxication (accidental or otherwise) is a known public health problem and its management/acute treatment adds strain to healthcare resource budgets. Prescriber, parent patient, caregiver education materials are useful tools to increase community awareness of the risk of paediatric intoxication.

Important Identified Risk: Hepatitis, Hepatic Events, Use in Patients with Hepatic Impairment	
Potential mechanisms	Many analgesics, including opioids, undergo hepatic metabolism (e.g., oxidation, dealkylation). Therefore, the potential for toxicity of these medications can increase in individuals with reduced hepatic function (Soleimanpour 2016). Buprenorphine is metabolised primarily by the liver, and plasma levels have been found to be higher for buprenorphine in individuals with moderate to severe hepatic impairment compared to healthy subjects. Infection is primarily secondary to IV drug abuse.
Evidence source(s) and strength of evidence	Section 4.4 of the SUBUTEX CCDS states that cases of acute hepatic injury have been reported in opioid dependent patients, both in clinical trials and in postmarketing adverse reaction reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of cytolytic hepatitis, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. In many cases, the presence of pre-existing mitochondrial impairment (genetic disease, liver enzyme abnormalities, viral infection such as hepatitis B and chronic hepatitis C, alcohol abuse, anorexia, concomitant use of other potentially hepatotoxic medicines, or ongoing drug use by injection) may have a causative or contributory role. The effect of hepatic impairment on the PK of sublingual buprenorphine has been evaluated in a PK study. While no clinically significant changes have been observed in subjects with mild hepatic impairment, the plasma levels have been shown to be higher and half-life values have been shown to be longer for buprenorphine in subjects with moderate to severe hepatic impairment.
Characterisation of risks	To date, 584 events classified as “Hepatitis, hepatic events” were reported with SUBUTEX (reporting rate 10.3 events per 100 000 patient years). To date, 4 583 events in patients with a history of hepatic disease have been reported with SUBUTEX. To date, 350 out of the 584 hepatic events were serious, 15 had a fatal outcome. To date, out of the 4 583 events reported in cases with a history of hepatic disease, 89 of these events had a fatal outcome.
Risk factors and risk groups	Patients who are positive for viral hepatitis or having existing liver dysfunction are at greater risk of liver injury. Injection drug users are at risk of contracting infectious diseases (EMCDDA 2017).
Preventability	Patients should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. SUBUTEX should be used with caution in patients with moderate to severe hepatic impairment. Baseline liver function tests and documentation of viral hepatitis status are recommended prior to commencing therapy. Patients who are positive for

	viral hepatitis, on concomitant medicinal products and/or have existing liver dysfunction are at greater risk of liver injury. Regular monitoring of liver function is recommended. When a hepatic event is suspected, further biological and etiological evaluation is required. Depending upon the findings, the medicinal product may be discontinued cautiously so as to prevent withdrawal symptoms and to prevent a return to illicit drug use. If the treatment is continued, hepatic function should be monitored closely.
Impact on the risk-benefit balance of the product	With the risk minimisation measures in place for the risk of hepatitis, hepatic events, use in patients with hepatic impairment, it is expected that the impact on the benefit-risk balance of SUBUTEX remains positive.
Public health impact	Hepatitis is a common health concern among opioid dependent injection drug users. However, the public health impact is low, as the risk can be largely minimised if the product is used as per the reference safety information.

Important Identified Risk: Use during Pregnancy, and Lactation (Effects on Newborn and Infant)	
Potential mechanisms	Buprenorphine is transferred across the placenta to the neonate (Farid 2008) thus, a foetus of a pregnant female using SUBUTEX can be exposed to buprenorphine. Chronic use of SUBUTEX by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions) in the neonate. Animal studies on buprenorphine demonstrate dose-related maternal, embryo, and foetal toxicity and dose-related behavioural changes in offspring, but no congenital malformations (Heel 1979). The primary outcomes included the number of neonates requiring treatment for NAS, the peak NAS score, the total amount of morphine needed to treat NAS, the length of hospital stay for neonates, and neonatal head circumference among the two groups. The results showed that pregnant women exposed to buprenorphine required significantly less morphine than did neonates exposed to methadone (mean total doses of 1.1 mg and 10.4 mg, respectively; $P < 0.0091$), and also had a significantly shorter hospital stay (10.0 vs. 17.5 days, respectively; $P < 0.0091$). The percentage of neonates requiring NAS treatment did not differ significantly between groups ($P=0.26$), nor did the groups differ significantly with respect to the peak NAS score ($P=0.04$) or head circumference ($P=0.04$) (Jones 2010).
Evidence(s) and strength of evidence	Section 4.8 of the SUBUTEX CCDS states that neonatal drug withdrawal syndrome has been reported among newborns of women who have received buprenorphine products during pregnancy. The syndrome may be milder and more protracted than that from short acting full μ-opioid agonists. The nature of the syndrome may vary depending upon the mother's drug use history. A PASS, PE-US001, was conducted to monitor pregnancy outcomes associated with exposure to SUBOXONE, SUBUTEX and methadone among pregnant opioid dependent women using medical registries in Sweden and Denmark from 2005 to 2011 (PE-US001). In Sweden, in general, women exposed to SUBUTEX or methadone more often delivered preterm and C section were more common, when compared to the total population. There were 34 infants with neonatal abstinence syndrome (NAS) exposed to SUBUTEX. In Denmark, among the 571 823 mothers who gave birth during the study period, 564 exposed infants in 557 pregnancies were identified. Compared with the nonexposed, all recorded opioid use was associated with greater prevalence of preterm birth prevalence ratios were 3.5 (95% CI: 0.6<20.1) in SUBUTEX exposed and low birth weight prevalence ratios 4.6

	(95% CI: 0.8<26.7) in SUBUTEX exposed. No stillbirths occurred in SUBUTEX only exposed pregnancies. A pregnancy assessment report was completed in 2013 that summarised all adverse event cases among women exposed to any buprenorphine product during pregnancy (SUBOXONE, SUBUTEX, TEMGESIC, LEPETAN, BUPRENEX or buprenorphine not otherwise specified) that were reported to INDV through 31 December 2012. A total of 7 268 individual case safety reports (ICSRs) from INDV's safety database, reported through 31 December 2012, were reviewed. The majority of these cases involved exposure to pregnancy without development of any adverse events. A total of 1 789 cases involved a pregnant woman/foetus or infant reported a targeted medical event (TME) of interest in pregnancy which were classified into the following categories: pregnancy loss; prematurity; other complications of pregnancy, labour/delivery and postpartum; congenital/foetal anomalies; NAS/neonatal drug withdrawal syndrome; other neonatal, infant and child conditions; developmental delay; and designated medical events. A comprehensive review of the TME case safety data from all sources, including post marketing surveillance of PhV reports and the scientific literature, did not identify any new or emerging safety concerns in relation to the use of buprenorphine or buprenorphine-naloxone combination medicinal products during pregnancy. Additionally, the MOTHER study was a double-blind, double-dummy, flexible dosing, parallel-group randomised clinical trial of the relative maternal and neonatal safety and efficacy of buprenorphine monotherapy (SUBUTEX) versus methadone for the treatment of opioid dependence during pregnancy. The primary outcomes included the number of neonates requiring treatment for NAS, the peak NAS score, the total amount of morphine needed to treat NAS, the length of hospital stay for neonates, and neonatal head circumference among the two groups. The results showed that neonates exposed to buprenorphine *in utero* required significantly less morphine than did neonates exposed to methadone (mean total doses of 1.1 mg and 10.4 mg, respectively; $P < 0.0091$), and also had a significantly shorter hospital stay (10.0 vs. 17.5 days, respectively; $P < 0.0091$). The percentage of neonates requiring NAS treatment did not differ significantly between groups (P=0.26), nor did the groups differ significantly with respect to the peak NAS score (P=0.04) or head circumference (P=0.04) (Jones 2010).
Characterisation of risks	To date, 5 301 AEs classified as "Use during pregnancy/lactation" were reported with SUBUTEX (reporting rate 93.9 events per 100 000 patient years). To date 3 206 of the 5 301 reported AEs associated with use during pregnancy or lactation were considered to be serious. Of these, 57 events had a fatal outcome. Chronic use of SUBUTEX by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions) in the neonate.
Risk factors and risk groups	Women with opioid use disorder may be affected by psychosocial and environmental factors including a history of sexual abuse and/or interpersonal violence, inadequate social supports, poor nutrition, unstable housing, and co-occurring psychiatric conditions (SAMHSA 2016).
Preventability	*Pregnancy*: Buprenorphine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Chronic use of SUBUTEX by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or

	convulsions) in the neonate. The syndrome is generally delayed for several hours to several days after birth. Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates. *Breastfeeding*: The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUBUTEX and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.
Impact on the risk-benefit balance of the product	With the risk minimisation measures in place for the risk of use during pregnancy/lactation (effects on newborn and infant), it is expected that the impact on the risk-benefit balance of SUBUTEX is low.
Public health impact	Buprenorphine use during pregnancy is known to contribute to neonatal drug withdrawal syndrome.

Important Identified Risk: CNS Depression	
Potential mechanisms	CNS depression is a pharmacological property of opioids.
Evidence sources(s) and strength of evidence	Respiratory depression may occur as a result of CNS depression and may lead to respiratory arrest and death. Any drug that has CNS depressant activity can add to the CNS depressant activity of buprenorphine. There has been a report of respiratory arrest during a clinical study (CR96/005) that involved the concomitant administration of SUBUTEX and other CNS depressants. While taking SUBUTEX, this patient severely overdosed on heroin and oxazepam which lead to the event of respiratory arrest. This case was considered possibly related to SUBUTEX. Section 4.4 of the SUBUTEX CCDS states that a number of cases of death due to respiratory depression have been reported, particularly when SUBUTEX was used in combination with benzodiazepines, when HDB was administered to non-opioid dependent individuals who had not developed a tolerance to the effects of opioids, or when buprenorphine was otherwise not used according to prescribing information. Epidemiological studies on opioids show little evidence of association between opioid use and crash risk (impairment of operating motorised machinery), in opioid dependent patients, whereas benzodiazepines, even at concentrations within the therapeutic range, are associated with increased crash risk (Schindler 2004). However, opioids combined with benzodiazepines, a preferred combination among polysubstance abusers, can significantly impair driving ability.
Characterisation of risk	In the available clinical trial data for SUBUTEX, 9 events classified as CNS depression were reported. Of these, there were 4 events of Road traffic accident/accident, 2 events each of Dizziness, and 1 event each of Vision blurred, Disturbance in attention and Thinking abnormal. In addition, 1 event classified as respiratory depression/respiratory failure was reported cumulatively. This event included the PT, Respiratory arrest. To date, 1 251 events classified as "CNS Depression" were reported with SUBUTEX (reporting rate 22.2 events per 100 000 patient years), including 474 events cumulatively associated with mental impairment as it relates to

	effect in driving ability (reporting rate 8.4 events per 100 000 patient years). Of these, 622 events were serious, and 43 events involved a fatal outcome. Of the 1 251 events, CNS depression-related events received for SUBUTEX, 528 events involved more than 1 type of CNS depressant.
Risk factors and risk groups	The risk for CNS depression is increased in patients who are on prescription medications for anxiety/depression and those with habitual alcohol intake. Risk factors for developing respiratory failure includes smoking tobacco products, excessive alcohol intake, a family history of respiratory disease or conditions, injury to the spine, brain, or chest, and immunocompromised patients (Macon 2017). Additionally, anyone driving under the influence of drugs, alcohol, or prescription or illicit CNS depressants are among the leading risk factors for traffic accidents. Young males are also at risk for substance abuse. Other risk factors include CNS depressants and respiratory illness.
Preventability	SUBUTEX may cause drowsiness, dizziness, or impaired thinking, especially during treatment induction and dose adjustment. If used with alcohol or CNS depressants (such as benzodiazepines, tranquilisers, sedatives or hypnotics) the effect is likely to be more pronounced. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities.
Impact on the risk-benefit impact of the product	With the risk minimisation measures in place for the risk of CNS depression, it is expected that the impact on the risk-benefit balance is low.
Public health impact	The potential public health impact of CNS depression with regard to effects on driving ability due to SUBUTEX is not known.

Important Potential Risk: Medication errors when switching between SUBUTEX/SUBOXONE and new buprenorphine-containing products (BCP) which are not interchangeable with SUBUTEX/SUBOXONE	
Potential mechanisms	The switching between BCPs which are not interchangeable may be necessary (e.g., if a person moves between care settings from the community in to prison or between prisons and doesn't need restabilisation). In addition, the risk for inadvertent substitution (prescribing and dispensing errors) may occur in the event of HCPs not being aware that Espranor and Zubsolv are not interchangeable with SUBUTEX/SUBOXONE or their generics. Different buprenorphine products have different bioavailability. Therefore, the dose in mg can differ between products. Once the appropriate dose has been identified for a patient with a certain product (brand), the product cannot readily be exchanged with another product.
Evidence source(s) and strength of evidence	Espranor (buprenorphine oral lyophilisate) is not interchangeable with other buprenorphine sublingual formulations at the same dose ("like for like" switch) as its bioavailability is 25-30% higher. The recommended starting dose of Espranor is 2 mg – 6 mg compared to 2 mg – 8 mg for other oral buprenorphine preparations and the maximum single daily dose for Espranor is 18 mg not 24 mg as with SUBUTEX. There is no 0.4 mg strength of Espranor, the lowest strength is 2 mg. The Espranor SmPC suggests that

	patients may need to be switched to 0.4 mg sublingual buprenorphine tablets to enable dose reduction (Section 4.2 of Espranor SmPC). Section 4.2 of the Espranor SmPC includes a boxed warning stating that 'Espanor is not interchangeable with other buprenorphine products. Different buprenorphine products have different bioavailability. Therefore, the dose in mg can differ between products. Once the appropriate dose has been identified for a patient with a certain product (brand), the product cannot readily be exchanged with another product' (Espranor SmPC, July 2017). Zubsolv is a rapidly disintegrating sublingual tablet containing 0.7 mg / 1.4 mg / 2.9 mg / 5.7 mg / 8.6 mg / 11.4 mg buprenorphine (as hydrochloride) and 0.18 mg / 0.36 mg / 0.71 mg / 1.4 mg / 2.1 mg / 2.9 mg naloxone (as hydrochloride dihydrate) as active substances. Development formulations were found to have improved absorption compared to the reference product, SUBOXONE. European Public Assessment Report (EPAR) for Zubsolv states that 'the differences between SUBOXONE and Zubsolv formulations imply that switching between the two *(at the same dose in mg)* would not reproduce the same plasma concentrations of buprenorphine. A lower buprenorphine exposure from Zubsolv may potentially result in reduced opioid receptor stimulation leading to withdrawal symptoms when switching from another buprenorphine product at a dose level below 5.7 mg/1.4 mg. In addition, owing to the long terminal half-life of buprenorphine, it would take several days to reach a new steady state when switching between formulations. This uncertainty supports the recommendation that patients should not switch between products. In the context of switching between SUBOXONE and Zubsolv products, the risk of under-dosing with secondary withdrawal symptoms is mitigated with amended guidance for switching formulation in Section 4.2 and 5.2 of the [Zubsolv] SmPC. In addition, in the clinical context, buprenorphine is individually titrated to clinical effect, and if small exposure differences between products were to translate to differences in clinical effects, this would be addressed by dose adjustments in the standard care of the patient'(Zubsolv: EPAR, January 2018). Section 4.2 of the Zubsolv SmPC includes a statement that 'Zubsolv is not interchangeable with other buprenorphine products, as different buprenorphine products have different bioavailability. Therefore, the dose in mg can differ between products. Once the appropriate dose has been identified for a patient with a specific buprenorphine product, that product should not be exchanged with another product. If a patient is changed between buprenorphine or buprenorphine and naloxone containing products, dose adjustments may be necessary due to the potential differences in bioavailability' (Zubsolv SmPC, March 2018). 'In comparative bioavailability studies, Zubsolv 11.4 mg/2.9 mg displayed equivalent buprenorphine exposure to 16 mg/4 mg (2 x 8 mg/2 mg) buprenorphine/naloxone administered as conventional sublingual tablets however Zubsolv 2 x 1.4 mg/0.36 mg displayed 20% lower buprenorphine exposure to 2 x 2 mg/0.5 mg buprenorphine/naloxone administered as conventional sublingual tablets' (Zubsolv SmPC, Section 5.2). Phase II clinical studies comparing safety and effectiveness of Espranor and SUBUTEX in opioid dependent patients suggest that administration of Espranor did not result in a higher risk of respiratory depression compared to SUBUTEX (Espranor Public Assessment Report, July 2015) . Adverse events in both healthy subjects and patient clinical studies were comparable between Zubsolv and SUBOXONE. The SAEs were consistent

	with the known safety profile for the buprenorphine/naloxone combination product (Zubsolv: EPAR, January 2018). Although the products are not bioequivalent, they are similar enough that switching is unlikely to result in severe consequences.
Characterisation of risks	To date, 16 events were reported in patients switching between SUBUTEX and Zubsolv (reporting rate 0.3 per 100 000 patient years). There were no cases reported that involved Espranor.
Risk factors and risk groups	Patients switching between SUBUTEX/SUBOXONE and Espranor or Zubsolv.
Preventability	The risk of inadvertent substitution due to prescribing and dispensing errors is mitigated through Espranor and Zubsolv labelling alerting HCPs and patients of the differences between the products. Patient's Brochure for use of BCP (distributed by pharmaceutical companies marketing BCP, under the authority of the ANSM) informs the patients that two presentations of buprenorphine: the sublingual tablet and the orodispersible lyophilisate are different and are not interchangeable. Based on existing Espranor and Zubsolv clinical studies, significant clinical concerns related to this transfer are not anticipated. Patients being switched between different formulations should be started on the corresponding dose compared to the previously administered product. Patients should be monitored for symptoms related to overdosing or under-dosing and dosing adjustments should be made as clinically indicated.
Impact on the risk-benefit balance of the product	It is expected that the impact on the risk-benefit balance is low.
Public health impact	It is expected that the public health impact is low.

SVII.3.2. Presentation of the Missing Information

Missing Information: Use in Children/Adolescents Less Than 15 Years Old

SUBUTEX may cause severe, possibly fatal, respiratory depression in children who accidentally ingest it. Children must be protected against exposure.

Use of SUBUTEX is contraindicated in children under 15 years (French SUBUTEX SmPC, June 2018).

Missing Information: Use in Elderly Patients (Greater Than or Equal To 65 Years Old)

The safety and efficacy of buprenorphine in elderly patients over 65 years of age have not been established.

Part II: Module SVIII - Summary of the Safety Concerns

Table 11: Summary of Safety Concerns for SUBUTEX

Important identified risks	• Fatal overdose (including severe respiratory failure [mechanism for death by overdose]) • Respiratory depression/respiratory failure • Misuse and/or abuse (injection/intranasal) • Paediatric intoxication • Hepatitis, hepatic events, use in patients with hepatic impairment • Use during pregnancy, and lactation (effects on newborn and infant) • CNS depression
Important potential risks	• Medication errors when switching between SUBUTEX/SUBOXONE and new buprenorphine-containing products (BCP) which are not interchangeable with SUBUTEX/SUBOXONE
Missing information	• Use in children/adolescents < 15 years old • Use in elderly patients (≥ 65 years old)

Part III: Pharmacovigilance Plan (Including Post-authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine PhV includes review of information regarding adverse events reported with the use of SUBUTEX from ICSR review, signal detection, aggregate reports review, and literature reviews.

Table 12: Routine Pharmacovigilance Activities

Fatal Overdose (including severe respiratory failure [mechanism for death by overdose])		
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Objectives
Ongoing monitoring of fatal overdose (including severe respiratory failure [mechanism for death by overdose]) as an important safety concern	Routine PhV	Monitor for a change in the nature, severity, or frequency of these events
Respiratory Depression/Respiratory Failure		
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Objectives
Ongoing monitoring of respiratory depression/respiratory failure as an important safety concern	Routine PhV	Monitor for a change in the nature, severity, or frequency of these events
Misuse and/or abuse (injection/intranasal)		
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Objectives
Ongoing monitoring of misuse and/or abuse (injection, intranasal) as an important safety concern	Routine PhV	Monitor for a change in the nature, severity, or frequency of these events
Paediatric intoxication		
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Objectives
Ongoing monitoring of paediatric intoxication as an important safety concern	Routine PhV	Monitor for a change in the nature, severity, or frequency of these events
Hepatitis, Hepatic Events, Use in Patients with Hepatic Impairment		
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Objectives
Ongoing monitoring of hepatitis, hepatic events, use in patients with hepatic impairment as an important safety concern	Routine PhV	Monitor for a change in the nature, severity, or frequency of these events
Use During Pregnancy and Lactation (effects on newborn and infant)		
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Objectives
Ongoing monitoring of use during pregnancy and lactation (effects on newborn and infant) as an important safety concern	Routine PhV	Monitor for a change in the nature, severity, or frequency of these events

CNS Depression		
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Objectives
Ongoing monitoring of CNS depression as an important safety concern	Routine PhV	Monitor for a change in the nature, severity, or frequency of these events
Medication errors when switching between SUBUTEX/SUBOXONE and new buprenorphine-containing products (BCP) which are not interchangeable with SUBUTEX/SUBOXONE		
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Objectives
Ongoing monitoring of the medication errors when switching between SUBUTEX/SUBOXONE and new BCP which are not interchangeable with SUBUTEX/SUBOXONE as an important safety concern	Routine PhV	Monitor for a change in the nature, severity, or frequency of these events
Missing Information: Use in Children/Adolescents Less Than 15 Years Old		
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Objectives
Ongoing monitoring of usage in paediatric patients (younger than 15 years old) as an important safety concern	Routine PhV	Monitor adverse events, detect, and evaluate signals among paediatric patients (younger than 15 years old) related to the use of SUBUTEX.
Missing Information: Use in Elderly Patients (Greater Than or Equal to 65 Years Old)		
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Objectives
Ongoing monitoring of usage in elderly patients as an important safety concern	Routine PhV	Monitor adverse events, detect, and evaluate signals among the elderly population related to the use of SUBUTEX

Routine PhV activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for SUBUTEX

Appendix 4 includes special interest group questionnaires for the purpose to obtain additional, structured information. These questionnaires will facilitate the capture of clinically relevant and complete information at the time of the initial report.

Other forms of routine PhV activities for any safety concerns.

No other forms of routine PhV activities are currently being conducted for any safety concerns for SUBUTEX.

III.2 Additional Pharmacovigilance Activities

There are no additional PhV activities planned to date to assess effectiveness of risk minimisation measures for SUBUTEX.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable

Part IV: Plans for Post-authorisation Efficacy Studies

There are currently no planned or ongoing post-authorisation efficacy studies for SUBUTEX that are conditions of the marketing authorisation or that are specific obligations.

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Table 13: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Fatal overdose	Routine risk communication: Section 4.4 of the SUBUTEX CCDS Routine risk minimisation activities recommending specific clinical measures to address the risk: To minimise the risk of misuse, abuse and diversion, appropriate precautions should be taken when prescribing and dispensing buprenorphine, such as to avoid prescribing multiple refills early in treatment, and to conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's level of stability. Buprenorphine should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis). Patients with the physical and/or pharmacological risk factors above should be monitored, and dose reduction may be considered. Other routine risk minimisation measures beyond the Product Information: Patient's Brochure for use of BCP (distributed by pharmaceutical companies marketing BCP, under the authority of the ANSM) alerts the patients that 'The risk of fatal overdose from respiratory depression increases if you take benzodiazepines, other opioids, or alcohol while you are taking it'.
Respiratory depression/Respiratory failure	Routine risk communication: Section 4.5 of the SUBUTEX CCDS Routine risk minimisation activities recommending specific clinical measures to address the risk: SUBUTEX should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis). SUBUTEX should not be used together with alcoholic drinks and must be used cautiously with medicines containing alcohol. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking SUBUTEX and should also be cautioned to use benzodiazepines concurrently with SUBUTEX only as prescribed. Other routine risk minimisation measures beyond the Product Information: Patient's Brochure for use of BCP (distributed by pharmaceutical companies marketing BCP, under the authority of the ANSM) alerts the patients that 'Taking soothing or sleeping medications (benzodiazepines and related drugs) while taking buprenorphine without medical advice is dangerous.

	Taking alcoholic beverages and even drugs containing alcohol is not recommended during buprenorphine therapy. The risk of fatal overdose from respiratory depression increases if you take benzodiazepines, other opioids, or alcohol while you are taking it'.
Misuse and/or abuse (injection/intranasal)	Routine risk communication: Sections 4.4, 4.5 and 6.4 of the SUBUTEX CCDS Routine risk minimisation activities recommending specific clinical measures to address the risk: To minimise the risk of misuse, abuse and diversion, appropriate precautions should be taken when prescribing and dispensing SUBUTEX, such as to avoid prescribing multiple refills early in treatment, and to conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's level of stability. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking SUBUTEX and should also be cautioned to use benzodiazepines concurrently with SUBUTEX only as prescribed. Protect children against exposure and keep out of reach and sight of children. Other routine risk minimisation measures beyond the Product Information: Patient's Brochure for use of BCP (distributed by pharmaceutical companies marketing BCP, under the authority of the ANSM) alerts the patients that injection or sniffing of buprenorphine is dangerous for their health, 'If you inject or sniff, you are at risk of overdose (respiratory failure), infections, liver damage and vascular lesions (injection), or nasal mucosal damage (sniff). The injection or the sniff do not allow to reach a stabilization of good quality, necessary condition for your wellbeing'.
Paediatric intoxication	Routine risk communication: Sections 4.4 and 6.4 of the SUBUTEX CCDS Routine risk minimisation activities recommending specific clinical measures to address the risk: SUBUTEX is only available in child-proof blister packs and the labelling clearly instructs to keep out of reach and sight of children. Buprenorphine may cause severe, possibly fatal, respiratory depression in children who accidentally ingest it. Use of SUBUTEX is contraindicated in children under 15 years (French SUBUTEX SmPC). Other routine risk minimisation measures beyond the Product Information: Patient's Brochure for use of BCP (distributed by pharmaceutical companies marketing BCP, under the authority of the ANSM) states 'Never take the medicine out of the box in advance. Do not take your medicine in front of children. Keep it in a safe place'.
Hepatitis, Hepatic Events, Use in Patients with Hepatic Impairment	Routine risk communication: Sections 4.2 and 4.4 of the SUBUTEX CCDS Routine risk minimisation activities recommending specific clinical measures to address the risk: Patients should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. SUBUTEX should be used with caution in patients with moderate to severe hepatic impairment. Baseline liver function tests and documentation of viral hepatitis status are recommended prior to commencing therapy. Patients who are positive for

	viral hepatitis, on concomitant medicinal products and/or have existing liver dysfunction are at greater risk of liver injury. Regular monitoring of liver function is recommended. When a hepatic event is suspected, further biological and etiological evaluation is required. Depending upon the findings, the medicinal product may be discontinued cautiously so as to prevent withdrawal symptoms and to prevent a return to illicit drug use. If the treatment is continued, hepatic function should be monitored closely. Other routine risk minimisation measures beyond the Product Information: Patient's Brochure for use of BCP (distributed by pharmaceutical companies marketing BCP, under the authority of the ANSM) instructs the patients to tell doctor immediately or seek medical attention urgently if side effects are developed such as severe fatigue, itching with yellowing of the skin or eyes (these may be symptoms of a liver injury).
Use during pregnancy (effects on newborn and infant)	Routine risk communication: Section 4.6 of the SUBUTEX CCDS Routine risk minimisation activities recommending specific clinical measures to address the risk: *Pregnancy*: Buprenorphine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Chronic use of SUBUTEX by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions) in the neonate. The syndrome is generally delayed for several hours to several days after birth. Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates. *Breastfeeding*: The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUBUTEX and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition. Other routine risk minimisation measures beyond the Product Information: Patient's Brochure for use of BCP (distributed by pharmaceutical companies marketing BCP, under the authority of the ANSM) informs the patients that 'Buprenorphine can be used during pregnancy with appropriate medical follow-up. Do not change your treatment without medical advice. Before breastfeeding, talk to your doctor about assessing your personal risk factors and whether you can breastfeed while taking this medicine'.
CNS Depression	Routine risk communication: Section 4.7 of the SUBUTEX CCDS Routine risk minimisation activities recommending specific clinical measures to address the risk: SUBUTEX may cause drowsiness, dizziness, or impaired thinking, especially during treatment induction and dose adjustment. If used with alcohol or CNS depressants the effect is likely to be more pronounced. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities. Other routine risk minimisation measures beyond the Product Information: Patient's Brochure for use of BCP (distributed by pharmaceutical companies marketing BCP, under the authority of the ANSM) alerts the patients that 'Taking soothing or sleeping medications (benzodiazepines and related drugs) while taking buprenorphine without medical advice is dangerous.

	Taking alcoholic beverages and even drugs containing alcohol is not recommended during buprenorphine therapy. Driving vehicles buprenorphine may cause drowsiness, dizziness or altered thinking. This can happen especially during the first weeks of treatment or when your dose is changed, but also if you consume alcohol or take other sedatives with buprenorphine'.
Medication errors when switching between SUBUTEX/SUBOXONE and new buprenorphine-containing products (BCP) which are not interchangeable with SUBUTEX/SUBOXONE	Routine risk communication: The risk of inadvertent substitution due to prescribing and dispensing errors is mitigated through Espranor and Zubsolv labelling alerting HCPs and patients of the differences between the products. Routine risk minimisation activities recommending specific clinical measures to address the risk: Based on existing Espranor and Zubsolv clinical studies, significant clinical concerns related to switching between SUBUTEX/SUBOXONE and Espranor or Zubsolv are not anticipated. Patients being switched between different formulations should be started on the corresponding dose compared to the previously administered product. Patients should be monitored for symptoms related to overdosing or under-dosing and dosing adjustments should be made as clinically indicated. Other routine risk minimisation measures beyond the Product Information: Patient's Brochure for use of BCP (distributed by pharmaceutical companies marketing BCP, under the authority of the ANSM) informs the patients that two presentations of buprenorphine: the sublingual tablet and the orodispersible lyophilisate are different and are not interchangeable.
Use in Children/Adolescents <15 years old	Routine risk communication: Sections 4.2, 4.4 and 6.4 of the SUBUTEX CCDS Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.4 states to protect children against exposure. Section 6.4 of the SUBUTEX CCDS states to keep out of reach and sight of children. Use of SUBUTEX is contraindicated in children under 15 years (French SUBUTEX SmPC). Other routine risk minimisation measures beyond the Product Information: None
Use in Elderly Patients (≥ 65 years old)	Routine risk communication: SUBUTEX CCDS Section 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.4 of the SUBUTEX CCDS states that opioids should be administered with caution to elderly or debilitated patients. Other routine risk minimisation measures beyond the Product Information: None

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of SUBUTEX.

V.3. Summary of Risk Minimisation Measures

Table 14: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Fatal overdose (including severe respiratory failure [mechanism for death by overdose])	Routine risk minimisation measures: Section 4.4 of SUBUTEX CCDS Additional risk minimisation measures: No additional risk minimisation measures	Routine PhV activities
Respiratory depression/Respiratory Failure	Routine risk minimisation measures: Section 4.5 of SUBUTEX CCDS Additional risk minimisation measures: No additional risk minimisation measures	Routine PhV activities
Misuse and/or abuse (injection/intranasal)	Routine risk minimisation measures: Sections 4.4, 4.5 and 6.4 of the SUBUTEX CCDS Additional risk minimisation measures: No additional risk minimisation measures	Routine PhV activities
Paediatric intoxication	Routine risk minimisation measures: Sections 4.4 and 6.4 of the SUBUTEX CCDS, Section 4.3 of the French SUBUTEX SmPC Additional risk minimisation measures: No additional risk minimisation measures	Routine PhV activities
Hepatitis, Hepatic Events, Use in Patients with Hepatic Impairment	Routine risk minimisation measures: Sections 4.2 and 4.4 of the SUBUTEX CCDS Additional risk minimisation measures: No additional risk minimisation measures	Routine PhV activities
Use during pregnancy/lactation (effects on newborn and infant)	Routine risk minimisation measures: Section 4.6 of the SUBUTEX CCDS Additional risk minimisation measures: No additional risk minimisation measures	Routine PhV activities
CNS depression	Routine risk minimisation measures: Section 4.7 of the SUBUTEX CCDS Additional risk minimisation measures: No additional risk minimisation measures	Routine PhV activities
Medication errors when switching between SUBUTEX/SUBOXONE and new buprenorphine-containing products (BCP) which are not	Routine risk minimisation measures: The risk of inadvertent substitution due to prescribing and dispensing errors is mitigated through Espranor and Zubsolv	Routine PhV activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
interchangeable with SUBUTEX/SUBOXONE	labelling alerting HCPs and patients of the differences between the products Additional risk minimisation measures: No additional risk minimisation measures	
Use in Children/Adolescents <15 years old	Routine risk minimisation measures: Sections 4.2, 4.4 and 6.4 of the SUBUTEX CCDS, Section 4.3 of the French SUBUTEX SmPC Additional risk minimisation measures: No additional risk minimisation measures	Routine PhV activities
Use in Elderly Patients (≥ 65 years old)	Routine risk minimisation measures: Section 4.4 of the SUBUTEX CCDS Additional risk minimisation measures: No additional risk minimisation measures	Routine PhV activities

Part VI: Summary of the Risk Management Plan

This is a summary of the RMP for SUBUTEX. The RMP details important risks of SUBUTEX, how these risks can be minimised, and how more information will be obtained about the SUBUTEX risks and uncertainties (missing information).

The product information for SUBUTEX provides essential information to healthcare professionals and patients on how SUBUTEX must be used.

Important new concerns or changes to the current concerns will be included in updates of the SUBUTEX RMP.

I. The Medicine and What it is Used For

SUBUTEX is indicated for the treatment of opioid dependence.

It is recommended that SUBUTEX treatment be prescribed as part of comprehensive management for opioid drug dependence.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of SUBUTEX, with measures to minimise such risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the product label addressed to patients and healthcare professionals.
- It can include important advice on the medicine's packaging.
- The authorised pack size and the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status, the way a medicine is supplied to the patient (e.g. with or without prescription), can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute routine PhV activities.

If important information that may affect the safe use of SUBUTEX is not yet available, it is listed under missing information below.

II.A List of important risks and missing information

Important risks of SUBUTEX are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of SUBUTEX. Potential risks are

concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 15: List of Important Risks and Missing Information for SUBUTEX

Important identified risks	• Fatal overdose (including severe respiratory failure [mechanism for death by overdose]) • Respiratory depression/respiratory failure • Misuse and/or abuse (injection/intranasal) • Paediatric intoxication • Hepatitis, hepatic events, use in patients with hepatic impairment • Use during Pregnancy, and lactation (effects on newborn and infant) • CNS depression
Important potential risks	• Medication errors when switching between SUBUTEX/SUBOXONE and new buprenorphine-containing products (BCP) which are not interchangeable with SUBUTEX/SUBOXONE
Missing information	• Use in children/adolescents < 15 years old • Use in elderly patients (≥ 65 years old)

II.B Summary of Important Risks

Table 16: Summary of Important Risks

Fatal Overdose (including severe respiratory failure [mechanism for death by overdose])	
Evidence for linking the risk to the medicine	Section 4.4 of the SUBUTEX CCDS states that a number of cases of death due to respiratory depression have been reported, particularly when SUBUTEX was used in combination with benzodiazepines, when high dose buprenorphine was administered to non-opioid dependent individuals who had not developed a tolerance to the effects of opioids, or when buprenorphine was otherwise not used according to prescribing information. Deaths have also been reported in association with concomitant administration of buprenorphine and other CNS depressants. Section 4.5 of the SUBUTEX CCDS states that a combination with benzodiazepines may result in death due to respiratory depression of central origin; which could lead to respiratory arrest and death. From the overdose study (PE-US003), recent figures at the EMCDDA recorded no buprenorphine-associated deaths in Denmark in their 2008-2011 reports. In Sweden, the fatal cases related to buprenorphine 15% had a filled prescription with SUBUTEX or SUBOXONE, 22% of the fatal methadone cases had filled prescription with methadone. The correlation between a fatal case related to buprenorphine and a filled prescription with SUBUTEX and SUBOXONE was hence relatively low and most of the

	subjects who died from a fatal overdose death by buprenorphine had obviously obtained the drug illegally.
Risk factors and risk groups	Patients abusing buprenorphine, especially IV abusers, polysubstance abusers, combining the use of buprenorphine with alcohol, benzodiazepines, and other drugs, are at high risk for overdose and associated respiratory depression. In substance-abuse treatment, SUBUTEX should be used with caution in patients with compromised respiratory function (e.g. chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis). Severe alcohol intoxication, alcohol withdrawal syndrome, and *delirium tremens* are associated with the risk of respiratory depression.
Risk minimisation measures	Routine risk minimisation measures: Supervised substance-abuse treatment on risk of death from SUBUTEX overdose is a major tool preventing overdose in SUBUTEX abusers. To minimise the risk of misuse, abuse and diversion, appropriate precautions should be taken when prescribing and dispensing buprenorphine, such as to avoid prescribing multiple refills early in treatment, and to conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's level of stability. Buprenorphine should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis). Patients with the physical and/or pharmacological risk factors above should be monitored, and dose reduction may be considered. Additional risk minimisation measures: None
Respiratory Depression/Respiratory Failure	
Evidence for linking the risk to the medicine	Section 4.4 of the SUBUTEX CCDS states that a number of cases of death due to respiratory depression have been reported, particularly when SUBUTEX was used in combination with benzodiazepines, when high dose buprenorphine was administered to opioid non-dependent individuals who had not developed tolerance to the effects of opioids, or when buprenorphine was otherwise not used according to prescribing information. Section 4.5 of the SUBUTEX CCDS states that a combination with benzodiazepines may result in death due to respiratory depression of central origin; which could lead to respiratory arrest and death. A case of respiratory arrest occurred during a clinical study (CR96/005) in which the patient severely overdosed on heroin and oxazepam that lead to the event of respiratory arrest. This case was considered possibly related to SUBUTEX.
Risk factors and risk groups	The risk for CNS depression is increased in patients who are on prescription medications for anxiety/depression and those with habitual alcohol intake. Risk factors for developing respiratory failure includes smoking tobacco products, excessive alcohol intake, a family history of

	respiratory disease or conditions, injury to the spine, brain, or chest, and immunocompromised patients (Macon 2017). Other risk factors include concomitant use of CNS depressants and respiratory illness.
Risk minimisation measures	Routine risk minimisation measures: SUBUTEX should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis). SUBUTEX should not be used together with alcoholic drinks and must be used cautiously with medicines containing alcohol. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking SUBUTEX and should also be cautioned to use benzodiazepines concurrently with SUBUTEX only as prescribed. Additional risk minimisation measures: None
Misuse and/or abuse (injection/intranasal)	
Evidence for linking the risk to the medicine	Opioids are the most commonly abused type of prescription drug and appear to be the largest contributor of increases in the prevalence of prescription drug abuse in the USA (McHugh 2015). Buprenorphine has been associated with life-threatening respiratory depression and death. Many, but not all, postmarketing reports regarding coma and death involved misuse by self-injection by the IV route or were associated with the concomitant use of buprenorphine and benzodiazepines or other CNS depressants, including alcohol. In cases of IV misuse, local reactions, systemic viral (HIV, HCV and HBV), microbial (endocarditis) [Cooper 2007, Chong 2009, Lee 2009], and fungal (*Candida endophthalmitis*) [Hirsbein 2008, Cazorla 2005, Aboltins 2005, Aguilar 1979, Cassoux 2002] infections, and sometimes septic reactions have been reported. Many of the histories provided from postmarketing data in France indicated that some or all of the drugs detected at post-mortem had probably been injected. The majority of the non-fatal cases of misuse, which came to medical attention (n=72) also included histories of injection misuse. Buprenorphine is relatively well absorbed by a nasal route (Lindhardt 2000), and intranasal buprenorphine abuse has been reported (Simojoki 2008). The most frequently reported postmarketing adverse event observed with buprenorphine sublingual tablets was drug misuse or abuse.
Risk factors and risk groups	Risk factors associated with opioid abusers include 18-25-year olds, the male gender, patients with psychiatric disorders (including depression and bipolar disorder), exposure to violence and sexual abuse, a patient with a history of substance abuse, and a family history of substance abuse (Brady 2016).

	Opioid and polysubstance abusers are at risk of IV and intranasal abuse of SUBUTEX. Sub-optimal treatment with SUBUTEX may prompt medication misuse by the patient, leading to overdose or treatment dropout.
Risk minimisation measures	Routine risk minimisation measures: To minimise the risk of misuse, abuse and diversion, appropriate precautions should be taken when prescribing and dispensing SUBUTEX, such as to avoid prescribing multiple refills early in treatment, and to conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's level of stability. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking SUBUTEX and should also be cautioned to use benzodiazepines concurrently with SUBUTEX only as prescribed. Additional risk minimisation measures: None
Paediatric Intoxication	
Evidence for linking the risk to the medicine	Due to limited amount of available data, patients below the age 15 should be closely monitored during treatment. A retrospective study reported 86 cases of buprenorphine overdose in children; 54 developed toxicity (UNECE 2007). Children who ingested >2 mg buprenorphine were more likely to experience a clinical effect; all who ingested >4 mg experienced some effect. In 54 children who developed toxicity, the clinical effects included drowsiness or lethargy (55%), miosis (21%), vomiting (21%), respiratory depression (7%), agitation or irritability (5%), pallor (3%), and coma (2%). No fatality was reported.
Risk factors and risk groups	Paediatric patients exposed to buprenorphine are likely to have a household member who is using buprenorphine, and in most cases, may be inadvertently (accidentally) exposed to it. Children who are exposed will exhibit signs and symptoms of opioid toxicity, including respiratory depression, altered mental status, miosis within 8 hours of reported exposure (Toce 2017). In older paediatric patients who may be opioid abusers and abusing buprenorphine, especially IV abusers, polysubstance abusers, combining the use of buprenorphine with alcohol, benzodiazepines, and other drugs, are at high risk for overdose and associated respiratory depression. In substance-abuse treatment, SUBUTEX should be used with caution in patients with compromised respiratory function (e.g. chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis)
Risk minimisation measures	Routine risk minimisation measures: SUBUTEX is only available in child-proof blister packs and the labelling clearly instructs to keep out of reach and sight of children. Buprenorphine may cause severe, possibly fatal, respiratory depression in children who accidentally ingest it. Use of SUBUTEX is contraindicated in children under 15 years (French SUBUTEX SmPC). Additional risk minimisation measures: None
Hepatitis, Hepatic Events, Use in Patients with Hepatic Impairment	

Evidence for linking the risk to the medicine	Section 4.4 of the SUBUTEX CCDS states that cases of acute hepatic injury have been reported in opioid dependent patients, both in clinical trials and in postmarketing adverse reaction reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of cytolytic hepatitis, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. In many cases, the presence of pre-existing mitochondrial impairment (genetic disease, liver enzyme abnormalities, viral infection such as hepatitis B and chronic hepatitis C, alcohol abuse, anorexia, concomitant use of other potentially hepatotoxic medicines, or ongoing drug use by injection) may have a causative or contributory role. The effect of hepatic impairment on the PK of sublingual buprenorphine has been evaluated in a PK study. While no clinically significant changes have been observed in subjects with mild hepatic impairment, the plasma levels have been shown to be higher and half-life values have been shown to be longer for buprenorphine in subjects with moderate to severe hepatic impairment.
Risk factors and risk groups	Patients who are positive for viral hepatitis or having existing liver dysfunction are at greater risk of liver injury. Injection drug users are at risk of contracting infectious diseases (EMCDDA 2017).
Risk minimisation measures	Routine risk minimisation measures: Patients should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. SUBUTEX should be used with caution in patients with moderate to severe hepatic impairment. Baseline liver function tests and documentation of viral hepatitis status are recommended prior to commencing therapy. Patients who are positive for viral hepatitis, on concomitant medicinal products and/or have existing liver dysfunction are at greater risk of liver injury. Regular monitoring of liver function is recommended. When a hepatic event is suspected, further biological and etiological evaluation is required. Depending upon the findings, the medicinal product may be discontinued cautiously so as to prevent withdrawal symptoms and to prevent a return to illicit drug use. If the treatment is continued, hepatic function should be monitored closely. Additional risk minimisation measures: None
Use during pregnancy/lactation (effects on newborn and infant)	
Evidence for linking the risk to the medicine	Section 4.8 of the SUBUTEX CCDS states that neonatal drug withdrawal syndrome has been reported among newborns of women who have received buprenorphine products during pregnancy. The syndrome may be milder and more protracted than that from short acting full μ-opioid agonists. The nature of the syndrome may vary depending upon the mother's drug use history. A PASS (PE-US001) was conducted to monitor pregnancy outcomes associated with exposure to SUBOXONE, SUBUTEX and methadone among pregnant opioid dependent women using medical registries in Sweden and Denmark from 2005 to 2011. In Sweden, in general, women exposed to SUBUTEX or methadone more often delivered preterm and C-sections were more common, when compared to the total population. There were 34 infants with NAS exposed to SUBUTEX. In Denmark, among the 571 823 mothers who gave birth during the study period; 564 exposed infants in 557 pregnancies were identified. Compared with the nonexposed, all recorded opioid use was associated with greater prevalence of preterm birth prevalence ratios were 3.5 (95% CI: 0.6<20.1) in SUBUTEX exposed

	and low birth weight (LBW) prevalence ratios 4.6 (95% CI: 0.8<26.7) in SUBUTEX exposed. No stillbirths occurred in SUBUTEX only exposed pregnancies. A pregnancy assessment report was completed in 2013 that summarised all adverse event cases among women exposed to any buprenorphine product during pregnancy (SUBOXONE, SUBUTEX, TEMGESIC, LEPETAN, BUPRENEX or buprenorphine not otherwise specified) that were reported to INDV through 31 December 2012. A total of 7 268 ICSRs from INDV's safety database, reported through 31 December 2012, were reviewed. The majority of these cases involved exposure to pregnancy without development of any adverse events. A total of 1 789 cases involved a pregnant woman/foetus or infant reported a TME of interest in pregnancy which were classified into the following categories: pregnancy loss; prematurity; other complications of pregnancy, labour/delivery and postpartum; congenital/foetal anomalies; NAS/neonatal drug withdrawal syndrome; other neonatal, infant and child conditions; developmental delay; and designated medical events. A comprehensive review of the TME case safety data from all sources, including postmarketing surveillance of PhV reports and the scientific literature, did not identify any new or emerging safety concerns in relation to the use of buprenorphine or buprenorphine-naloxone combination medicinal products during pregnancy. Additionally, the MOTHER study was a double-blind, double-dummy, flexible dosing, parallel-group randomised clinical trial of the relative maternal and neonatal safety and efficacy of buprenorphine monotherapy (SUBUTEX) versus methadone for the treatment of opioid dependence during pregnancy. The primary outcomes included the number of neonates requiring treatment for NAS, the peak NAS score, the total amount of morphine needed to treat NAS, the length of hospital stay for neonates, and neonatal head circumference among the two groups. The results showed that neonates exposed to buprenorphine *in utero* required significantly less morphine than did neonates exposed to methadone (mean total doses of 1.1 mg and 10.4 mg, respectively; P < 0.0091), and also had a significantly shorter hospital stay (10.0 vs. 17.5 days, respectively; P < 0.0091). The percentage of neonates requiring NAS treatment did not differ significantly between groups (P=0.26), nor did the groups differ significantly with respect to the peak NAS score (P=0.04) or head circumference (P=0.04) (Jones 2010).
Risk factors and risk groups	Women with opioid use disorder may be affected by psychosocial and environmental factors including a history of sexual abuse and/or interpersonal violence, inadequate social supports, poor nutrition, unstable housing, and co-occurring psychiatric conditions (SAMHSA 2016).
Risk minimisation measures	Routine risk minimisation measures: *Pregnancy*: Buprenorphine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Chronic use of SUBUTEX by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions) in the neonate. The syndrome is generally delayed for several hours to several days after birth. Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates.

	Breastfeeding: The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUBUTEX and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition. Additional risk minimisation measures: None
CNS Depression	
Evidence for linking the risk to the medicine	Respiratory depression may occur as a result of CNS depression and may lead to respiratory arrest and death. Any drug that has CNS depressant activity can add to the CNS depressant activity of buprenorphine. There has been a report of respiratory arrest during a clinical study (CR96/005) that involved the concomitant administration of SUBUTEX and other CNS depressants. While taking SUBUTEX, this patient severely overdosed on heroin and oxazepam which lead to the event of respiratory arrest. This case was considered possibly related to SUBUTEX. Section 4.4 of the SUBUTEX CCDS states that a number of cases of death due to respiratory depression have been reported, particularly when SUBUTEX was used in combination with benzodiazepines, when HDB was administered to non-opioid dependent individuals who had not developed a tolerance to the effects of opioids, or when buprenorphine was otherwise not used according to prescribing information. Epidemiological studies on opioids show little evidence of association between opioid use and crash risk (impairment of operating motorised machinery), in opioid dependent patients, whereas benzodiazepines, even at concentrations within the therapeutic range, are associated with increased crash risk (Schindler 2004). However, opioids combined with benzodiazepines, a preferred combination among polysubstance abusers, can significantly impair driving ability.
Risk factors and risk groups	The risk for CNS depression is increased in patients who are on prescription medications for anxiety/depression and those with habitual alcohol intake. Risk factors for developing respiratory failure includes smoking tobacco products, excessive alcohol intake, a family history of respiratory disease or conditions, injury to the spine, brain, or chest, and immunocompromised patients (Macon 2017). Additionally, anyone driving under the influence of drugs, alcohol, or prescription or illicit CNS depressants are among the leading risk factors for traffic accidents. Young males are also at risk for substance abuse. Other risk factors include CNS depressants and respiratory illness.
Risk minimisation measures	Routine risk minimisation measures: SUBUTEX may cause drowsiness, dizziness, or impaired thinking, especially during treatment induction and dose adjustment. If used with alcohol or CNS depressants (such as benzodiazepines, tranquilisers, sedatives or hypnotics) the effect is likely to be more pronounced. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities. Additional risk minimisation measures: None

Medication errors when switching between SUBUTEX/SUBOXONE and new buprenorphine-containing products (BCP) which are not interchangeable with SUBUTEX/SUBOXONE	
Evidence for linking the risk to the medicine	The switching between buprenorphine-containing products which are not interchangeable may be necessary (e.g., if a person moves between care settings from the community in to prison or between prisons and doesn't need restabilisation). In addition, the risk for inadvertent substitution (prescribing and dispensing errors) may occur in the event of HCPs not being aware that Espranor and Zubsolv are not interchangeable with SUBUTEX/SUBOXONE or their generics. Espranor (buprenorphine oral lyophilisate) is not interchangeable with other buprenorphine sublingual formulations at the same dose ("like for like" switch) as its bioavailability is 25-30% higher. The recommended starting dose of Espranor is 2 mg – 6 mg compared to 2 mg – 8 mg for other oral buprenorphine preparations and the maximum single daily dose for Espranor is 18 mg, not 24 mg as with SUBUTEX. There is no 0.4 mg strength of Espranor, the lowest strength is 2 mg. The Espranor SmPC suggests that patients may need to be switched to 0.4 mg sublingual buprenorphine tablets to enable dose reduction (Section 4.2 of Espranor SmPC). Section 4.2 of the Espranor SmPC includes a boxed warning stating that 'Espanor is not interchangeable with other buprenorphine products. Different buprenorphine products have different bioavailability. Therefore, the dose in mg can differ between products. Once the appropriate dose has been identified for a patient with a certain product (brand), the product cannot readily be exchanged with another product' (Espranor SmPC, July 2017). Patient's Brochure for use of BCP (distributed by pharmaceutical companies marketing BCP, under the authority of the ANSM) states that 'There are 2 presentations of buprenorphine: the sublingual tablet and the orodispersible lyophilisate. These 2 formulations are different and are not interchangeable. Always follow your doctor's prescription. Not to exchange the sublingual and orodispersible forms of buprenorphine'. Zubsolv is a rapidly disintegrating sublingual tablet containing 0.7 mg / 1.4 mg / 2.9 mg / 5.7 mg / 8.6 mg / 11.4 mg buprenorphine (as hydrochloride) and 0.18 mg / 0.36 mg / 0.71 mg / 1.4 mg / 2.1 mg / 2.9 mg naloxone (as hydrochloride dihydrate) as active substances. Development formulations were found to have improved absorption compared to the reference product SUBOXONE. The EPAR for Zubsolv states that 'the differences between SUBOXONE and Zubsolv formulations imply that switching between the two *(at the same dose in mg)* would not reproduce the same plasma concentrations of buprenorphine. A lower buprenorphine exposure from Zubsolv may potentially result in reduced opioid receptor stimulation leading to withdrawal symptoms when switching from another buprenorphine product at a dose level below 5.7 mg/1.4 mg. In addition, owing to the long terminal half-life of buprenorphine, it would take several days to reach a new steady state when switching between formulations. This uncertainty supports the recommendation that patients should not switch between products. In the context of switching between SUBOXONE and Zubsolv products, the risk of under-dosing with secondary withdrawal symptoms is mitigated with amended guidance for switching formulation in Section 4.2 and 5.2 of the [Zubsolv] SmPC. In addition, in the clinical context, buprenorphine is individually titrated to clinical effect, and if small exposure differences between products were to translate to differences in clinical effects, this would be addressed by dose adjustments in the

	standard care of the patient' (Espranor Public Assessment Report, July 2015). Section 4.2 of the Zubsolv SmPC includes a statement that 'Zubsolv is not interchangeable with other buprenorphine products, as different buprenorphine products have different bioavailability. Therefore, the dose in mg can differ between products. Once the appropriate dose has been identified for a patient with a specific buprenorphine product, that product should not be exchanged with another product. If a patient is changed between buprenorphine or buprenorphine and naloxone containing products, dose adjustments may be necessary due to the potential differences in bioavailability'. 'In comparative bioavailability studies Zubsolv 11.4 mg/2.9 mg displayed equivalent buprenorphine exposure to 16 mg/4 mg (2 x 8 mg/2 mg) buprenorphine/naloxone administered as conventional sublingual tablets however Zubsolv 2 x 1.4 mg/0.36 mg displayed 20% lower buprenorphine exposure to 2 x 2 mg/0.5 mg buprenorphine/naloxone administered as conventional sublingual tablets' (Zubsolv SmPC, Section 5.2). Phase II clinical studies comparing safety and effectiveness of Espranor and SUBUTEX in opioid dependent patients suggest that administration of Espranor did not result in a higher risk of respiratory depression compared to SUBUTEX (Espranor Public Assessment Report, July 2015). Adverse events in both healthy subjects and patient clinical studies were comparable between Zubsolv and SUBOXONE. The SAEs were consistent with the known safety profile for the buprenorphine/naloxone combination product (Espranor Public Assessment Report, July 2015) . Although the products are not bioequivalent, they are similar enough that switching is unlikely to result in severe consequences.
Risk factors and risk groups	Patients switching from SUBUTEX/SUBOXONE to Espranor or Zubsolv.
Risk minimisation measures	Routine risk minimisation measures: The risk of inadvertent substitution due to prescribing and dispensing errors is mitigated through Espranor and Zubsolv labelling alerting HCPs and patients of the differences between the products. Based on existing Espranor and Zubsolv clinical studies, significant clinical concerns related to this transfer are not anticipated. Patients being switched between different formulations should be started on the corresponding dose compared to the previously administered product. Patients should be monitored for symptoms related to overdosing or under-dosing and dosing adjustments should be made as clinically indicated. Additional risk minimisation measures: None
Use in Children/Adolescents Less Than 15 Years Old	
Risk minimisation measures	Routine risk minimisation measures: Children must be protected against exposure. Keep out of reach and sight of children. Use of SUBUTEX is contraindicated in children under 15 years (French SUBUTEX SmPC).

	Additional risk minimisation measures: None
Use in Elderly (Patients Greater Than or Equal To 65 Years Old)	
Risk minimisation measures	Routine risk minimisation measures: Opioids should be administered with caution to elderly or debilitated patients. Additional risk minimisation measures: None

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of SUBUTEX.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for SUBUTEX.

Part VII: Annexes

Annex 1 – EudraVigilance Interface

Not Applicable.

Annex 2 – Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Programme

Not applicable, since there are no additional PhV activities proposed in Part III of this RMP.

Annex 3 – Protocols for Proposed, On-going and Completed Studies in the Pharmacovigilance Plan

Not applicable

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

SPECIAL INTEREST QUESTIONS FOR BUPRENORPHINE CONTAINING PRODUCT

FATAL OVERDOSE

1. Please specify if an autopsy was done. If yes, please provide autopsy results and toxicology report. If not, please provide possible primary cause of death.

2. Please specify if product *[name of INDV product(s) or name of active ingredient(s)]* was identified as being in the patient's/subject's system. If yes, please specify the dose and route of administration.

3. Was there a reported cause of death? If so, please provide.

4. Is there any evidence to suggest that the overdose was intentional or accidental? What were the circumstances surrounding the overdose (e.g. party, binging, suicidal intent)?

5. What were the symptoms of the fatal overdose? Was there severe respiratory insufficiency? Please describe the event.

6. Did the patient/subject have any prior episode of overdose?

7. Please provide relevant medical history (e.g. asthma, COPD, respiratory distress, etc.)? If so, please describe.

8. What other drugs were being taken (prescription medications, street drugs, over-the-counter medications, herbal supplements, alcohol)? Please include name, indication for use, dose, frequency, start/stop date?

9. Please specify if the patient/subject took benzodiazepines and/or consumed alcohol and/or any other CNS depressant along with product.

10. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

OVERDOSES INVOLVING BENZODIAZEPINES AND/OR ALCOHOL

1. Please clarify what drug was overdosed. What were the symptoms of overdose? Does the patient/subject have symptoms of respiratory insufficiency?

2. Did the patient/subject have any prior episode of overdose?

3. What other drugs were being taken (prescription medications, street drugs, over the counter medications, herbal supplements, alcohol)? Please include name, indication for use, dose, frequency, start/stop date.

4. Were benzodiazepines and/or alcohol taken along with product *[name of INDV product(s) or name of active ingredient(s)]*?

5. Please provide product dosing information, including frequency and start/stop dates.

6. Was the patient/subject sent to the ER? Was he/she admitted to the hospital?

7. Was any treatment received? If so, please describe the treatment given.

8. Did the patient/subject recover and symptoms resolve? If so, please provide resolution dates. If the overdose was fatal, was an autopsy performed?

9. (ask only if fatal overdose) If an autopsy was performed, [please provide autopsy and toxicology findings (for HCP reporters)] or [may we request a copy of the autopsy report (for consumer reporters)].

10. Please provide any significant prior medical history.

11. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

DEATH

1. Please provide the cause of death.

2. Please confirm the date of death.

3. Was an autopsy performed? Please provide a copy of the autopsy report or death certificate and/or toxicology results, if available. What was the primary cause of death?

4. Please confirm if patient/subject was on product *[name of INDV product(s) or name of active ingredient(s)]* at the time of death? Please provide product dosing information and start/stop dates.

5. Please specify if the patient/subject had any past medical history of any major disorder (e.g. cardiac disorder, renal disorder, hepatic disorder, history of cancer, etc.)

6. Please provide concomitant medication(s) dosing information (including recreational drugs, herbal medications and supplements).

7. Please specify if the patient/subject had a history of any addiction (e.g. alcohol consumption, smoking, or drug dependence).

8. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

RESPIRATORY DEPRESSION/RESPIRATORY FAILURE

1. Please specify if the event started after or before the intake of product *[name of INDV product(s) or name of active ingredient(s)]*.

2. What were the signs and symptoms? (e.g. inability to breathe, bluish coloration in the skin, restlessness, anxiety, confusion, altered consciousness, rapid shallow breathing, racing heart, profuse sweating, etc.)

3. When did the symptom of respiratory depression/respiratory failure occur? Please provide start and stop dates.

4. Please specify the dosage, route of administration, frequency and strength of the product given to the patient/subject.

5. Was there a history of breathing problems before the event (e.g. asthma, COPD or other respiratory diseases)?

6. Please specify if the patient/subject have any family history of any respiratory problem (e.g. asthma, COPD or other respiratory diseases)?

7. Was there a history of use of alcohol or other CNS depressants (e.g. benzodiazepines)? If so, please provide dosing information.

8. Was there an event of CNS depression?

9. What treatment was received for the event of respiratory depression/respiratory failure and what was the outcome? Please provide the resolution date.

10. Has product been taken since the event of respiratory depression/respiratory failure? If yes, did respiratory depression/respiratory failure reoccur?

11. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

MISUSE/ABUSE

1. How is product *[name of INDV product(s) or name of active ingredient(s)]* being used (e.g. injection, intranasal, etc.) and for how long? What was it prescribed for?

2. If taking product not as prescribed (e.g. injection, intranasal, etc.), have there been any unfavorable side effects? If yes, what symptoms have been experienced?

3. How was product obtained (e.g. prescription, obtained from a friend, bought off the street)?

4. What dose of product was being used?

5. What other medications/substances have been used (e.g. alcohol, benzodiazepines, or other opioids such as methadone, oxycontin, vicodin, etc.)?

6. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

PAEDIATRIC ACCIDENTAL EXPOSURE / PAEDIATRIC INTOXICATION

1. How old was the child exposed to product *[name of INDV product(s) or name of active ingredient(s)]*?

2. Please specify the dosage, route of administration, frequency and strength of the product child was exposed to.

3. What signs and symptoms did the child experience and for how long?

4. Was a physician seen? Was treatment received? If so, provide treatment details.

5. Did the child require lifesaving equipment for the treatment of intoxication?

6. Was the child hospitalised? If so, please provide dates of hospitalisation and discharge.

7. Did the child recover? If so please provide the resolution date along with treatment received and outcome.

8. Was there any additional drug along with product child exposed to? If yes, please provide the dosage, route of administration, frequency and strength.

9. How many times was the child exposed?

10. Does the child still have any symptoms now?

11. How is the child overall growing and meeting all milestones?

12. If a consumer report, may we contact the child's physician/paediatrician? If yes, please provide name and contact information.

HEPATIC EVENTS / DRUG RELATED HEPATIC DISORDERS

1. Were baseline liver function tests done prior to starting product *[name of INDV product(s) or name of active ingredient(s)]*? If yes, please provide results.

2. Did the hepatic enzymes increase after taking product? Please provide lab results (e.g. AST, ALT, ALP, total bilirubin, INR). If yes, on which day after the start on product were the increased enzymes detected?

3. Did the event result in an ER visit or hospitalisation? If yes, what was the duration of hospitalisation?

4. Please specify if the patient/subject underwent any additional relevant laboratory/diagnostic investigations. If yes, please specify the findings.

5. Is there a history of hepatitis (e.g. Hepatitis A, B or C, etc.), HIV infection, or any other viral infection? If so, please provide relevant medical history and/or relevant treatment/concomitant medications.

6. Please specify if the patient/subject consumed alcohol. If so, how much a day and for how long.

7. Please specify the dosage, route of administration, frequency and strength of product given to the patient/subject.

8. Was product stopped after hepatic enzymes increased? If yes, did the event resolve? If yes, please provide the date of resolution. What was the outcome?

9. Was product restarted after the event resolved? If yes, did the hepatic enzymes increase after the re-start of product?

10. Please specify if the patient/subject was taking any hepatotoxic drugs (e.g. acetaminophen, aspirin, NSAIDs, steroids, antibiotics, oral contraceptives, statins, herbal medicines, etc.) before the onset of hepatic event. If yes, please provide medication's dose and start/stop dates.

11. Please specify if the patient/subject underwent any relevant laboratory/diagnostic investigations. If yes, please specify the findings.

12. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

PREGNANCY

1. Please provide start/stop dates, dose, frequency and route of product *[name of INDV product(s) or name of active ingredient(s)]* since initial start date (including any dosing changes).

2. Was there any switch of drugs (e.g. Suboxone to Subutex) or change in dosage of medication (e.g. 6 to 12 mg) during pregnancy? Please provide details. Also, when did the switch of drug or change in dosage occur during the pregnancy? e.g. (first/second/third trimester).

3. Please confirm and provide last menstrual period and expected date of delivery.

4. Please provide relevant pregnancy history (e.g. previous pregnancies, outcomes, complications, miscarriages, births, delivery complications, congenital defects during previous pregnancies (if any), etc.)

5. Please provide relevant maternal medical history (e.g. diabetes, hypertension, etc.)

6. Were any prescription medications, over-the-counter drugs, herbal supplements, recreational drugs, alcohol or tobacco consumed during pregnancy? If so, what, how much? Was the medication/drug/alcohol/tobacco stopped? During what trimester of pregnancy?

7. Is there a family history of birth defects? If so, what were the birth defects?

8. What was the outcome of the delivery (e.g. normal vaginal birth, emergent caesarean section, elective caesarean section, induced labor)? Premature or full term? Miscarriage or elective abortion? If miscarriage, how many weeks' gestation?

9. Please provide the baby's date of birth, sex, weight, length and APGAR scores, if available along with gestation age at birth (in weeks).

10. During pre-natal visits, were there any abnormal maternal or foetal findings?

11. Did patient/subject or baby develop any respiratory symptoms? If so, what were the symptoms? What was the treatment and outcome? Please include the date of resolution/recovery.

12. Did the baby have neonatal withdrawal? If so, what were the symptoms?

13. Did the baby require prolonged hospitalisation or treatment? If yes, what exactly was the reason for prolonged hospitalisation? What was the treatment and outcome? Please provide dates of delivery, discharge and resolution/recovery.

14. Has the baby experienced any feeding problems? Has he/she met growth and development milestones to date? May we contact patient/subject for a two-year follow-up to obtain information about the baby's growth and developmental milestones?

15. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

BREASTFEEDING (LACTATION)

1. Did mother breastfeed? For how long? Did she switch back to product *[name of INDV product(s) or name of active ingredient(s)]* while breastfeeding?

2. Were there any problems experienced during breastfeeding?

3. Did baby have any developmental delays or symptoms of withdrawal after breastfeeding was stopped?

4. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

MISCARRIAGES (SPONTANEOUS ABORTIONS)

1. Please provide/confirm last menstrual period (LMP) and expected date of delivery (EDD).

2. Please provide start/stop dates of product *[name of INDV product(s) or name of active ingredient(s)]*. Please specify the dosing information.

3. Was there any switch of drugs (e.g. Suboxone to Subutex) or change in dosage of medication (e.g. 6 to 12 mg) during pregnancy? Please provide details. Also, when did the switch of drug or change in dosage occur during the pregnancy? e.g. (first/second/third trimester).

4. Please specify the total weeks of gestation at the time of spontaneous abortion/miscarriage.

5. Please provide relevant pregnancy history (e.g. previous pregnancies, outcomes, complications, miscarriages, births, delivery complications, congenital defects during previous pregnancies, etc.)

6. Was there any physical trauma to the abdomen prior to the miscarriage (e.g. fall, traffic accident, etc.)? If so, how long before the miscarriage did the physical trauma occur?

7. Please specify if there were any reproductive abnormalities (e.g. uterine fibroid, ectopic pregnancy).

8. Please provide relevant maternal medical history (e.g. diabetes, hypertension, thyroid disorder, etc.)

9. Please specify if patient/subject had family history of any congenital disorder such as birth defects in the family, etc. If so, what were the congenital defects?

10. Please specify if the patient/subject has history of tobacco use/alcohol consumption. If yes, please specify on an average how much tobacco used each day/week or how much alcohol is consumed each day/week.

11. Please specify if the patient/subject had a history of use of drugs such as cocaine, cannabis, LSD, high dose of caffeine, etc.

12. Please specify if the patient/subject underwent any relevant laboratory/diagnostic investigations. If yes, please specify the findings.

13. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

NEONATAL WITHDRAWAL

1. What medications were taken during the pregnancy? Please include name, dose, frequency and indication used for.

2. When was product *[name of INDV product(s) or name of active ingredient(s)]*?

3. Did the mother have a recent switch of medications (e.g. methadone to Suboxone tablet/film, Suboxone tablet to Suboxone film, Subutex to Suboxone tablet, Suboxone/Subutex to generic Suboxone, etc.)?

4. What were the signs and symptoms of neonatal withdrawal (agitation, apnoea, blood pressure increased, bradycardia, convulsion, crying, dehydration, diarrhoea)?

5. Was there a change in dosing (e.g. 16 mg to 24 mg)? If yes, please provide start date of new dosage and stop date of previous dosage.

6. When was the neonate diagnosed with withdrawal? Was diagnosis made by a physician?

7. How severe were the withdrawal symptoms (e.g. mild, moderate, severe)?

8. Was treatment received for withdrawal? If so, please provide name, dose, start/stop dates of treatment.

9. How long was the baby in the hospital due to withdrawal?

10. Did all of the symptoms resolve prior to discharge?

11. Is the baby feeding well and meeting growth and development milestones?

12. If a consumer report, may we contact your physician and/or paediatrician? If yes, please provide name and contact information.

CNS DEPRESSION

1. Please specify if the event started after or before the intake of product *[name of INDV product(s) or name of active ingredient(s)]*.

2. What were the signs and symptoms? (e.g. drowsiness, dizziness, blurred vision, impaired thinking, etc.)

3. Did the symptom(s) of CNS depression affect the ability to drive?

4. During treatment with product, has the patient/subject been involved in any road traffic accidents while driving?

5. When did the symptom(s) of CNS depression occur? Please provide start and stop dates.

6. How severe were the CNS depression symptoms (e.g. mild, moderate, or severe)?

7. Please specify the dosage, route of administration, frequency and strength of the product given to the patient/subject.

8. Was there a history of concomitant use of alcohol or other CNS depressants (e.g. benzodiazepines)? If so, please provide details, including indication and dosing information.

9. Please specify if the patient/subject has a past medical history or concurrent medical condition of any CNS disorders.

10. What treatment was received for the event of CNS depression and what was the outcome? Please provide the resolution date, if available.

11. Has product been taken since the event of CNS depression? If yes, did CNS depression reoccur?

12. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

ELDERLY POPULATION

1. Please specify the event(s) the patient/subject experienced at the time of reporting.

2. Please specify if the patient/subject presented with the event(s) prior to starting product *[name of INDV product(s) or name of active ingredient(s)]*.

3. Please specify if the event(s) worsened since starting product.

4. Please specify if the patient/subject has any history of psychiatric illness/medical illness (diabetes, hypertension etc.), hospitalisations, operations, drug use etc. If yes, please specify the illness, duration and if it is still ongoing/recovered.

5. Please specify the dosage, route of administration, frequency and strength of the product given to the patient/subject.

6. Please specify if the patient/subject has a history of tobacco use i.e. chewing/smoking etc. If yes, please specify on an average how many cigarettes are smoked each day/week or how many times tobacco is chewed each day/week.

7. Please specify if the patient/subject consumes alcohol. If yes, for how long and how much per day?

8. Please specify if the patient/subject had a history of use of drugs such as cocaine, cannabis, LSD, amphetamine, etc.

9. Please specify the treatment or any other concomitant medication(s) that the patient/subject was taking. Please specify the start date, stop date and action taken.

10. Did the patient/subject stop taking product? If yes, please specify if the patient's/subject's condition improved after stopping the drug.

11. Please specify if the patient/subject underwent any relevant laboratory/diagnostic investigations. If yes, please specify the findings.

12. Please specify final outcome of the event(s) (e.g. completely recovered, condition improving, not recovered, etc.)

13. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

OFF-LABEL USE

1. Please specify the dosage, route of administration, frequency and strength of the product *[name of INDV product(s) or name of active ingredient(s)]* given to the patient/subject.

2. (**only if reported as "off label use"**) What was the type of off label use (unapproved indication, unapproved age group, unapproved dosage or dosing regimen, or unapproved route of administration)? Please explain.

3. Is the off label use of product still continuing?

4. Has/did the patient/subject experience any adverse event due to off label use? If yes, please describe in detail.

5. Did this off label use result in an ER visit or hospitalisation? If yes, what was the duration of hospitalisation?

6. Is the patient on any other medications or illicit drugs? If yes, please provide medication's dose and start/stop dates.

7. If a consumer reports, may we contact your physician? If yes, please provide name and contact information.

MEDICATION ERROR

1. Please specify the dosage, route of administration, frequency and strength of the product *[name of INDV product(s) or name of active ingredient(s)]* given to the patient/subject.

2. What type of medication error patient/subject experienced (e.g. related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, dispensing, distribution, or administration)?

3. Did the patient/subject recently switch from one buprenorphine formulation to another (e.g. SUBUTEX/SUBOXONE to Zubsolv)?

4. Does patient/subject experience any adverse event due to medication error. If yes, what were the signs and symptoms?

5. Does patient/subject experienced lack of drug effect due to medication error. If yes, please describe in detail.

6. Were any other medication(s) or agent started with product (concomitant medication). If yes, please provide dose and start/stop dates of concomitant medication(s).

7. Did this medication error result in an ER visit or hospitalisation? If yes, what was the duration of hospitalisation?

8. What was the next step taken after the event of medication error?

9. If a consumer reports, may we contact your physician? If yes, please provide name and contact information.

DRUG INTERACTIONS

1. Please specify the dosage, route of administration, frequency and strength of the product *[name of INDV product(s) or name of active ingredient(s)]* given to the patient/subject.

2. What type of drug interactions patient/subject experienced (e.g. drug-drug interaction, drug-food interactions, or drug interaction with some agent)?

3. Were any other medication(s) or agent started with product (concomitant medication). If yes, please provide dose and start/stop dates of concomitant medication(s).

4. What were the signs and symptoms of drug interactions?

5. How long was the duration between the administration of product and appearance of signs and symptoms of drug interactions?

6. How severe was drug interaction (e.g. mild, moderate, or severe)?

7. Does patient/subject experience any adverse event due to drug interactions. If yes, what were the signs and symptoms?

8. Does patient/subject experienced lack of drug effect due to drug interactions. If yes, please describe in detail.

9. Did patient/subject receive any treatment for drug interaction? If yes, please describe in detail.

10. Did this drug interactions result in an ER visit or hospitalisation? If yes, what was the duration of hospitalisation?

11. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

LACK OF DRUG EFFECT

1. Please specify the dosage, route of administration, frequency and strength of product *[name of INDV product(s) or name of active ingredient(s)]* given to the patient/subject.

2. What were the signs and symptoms indicating a lack of drug effect?

3. Has the patient/subject experienced lack of drug effect in past for this product?

4. Please specify if the patient/subject has any family history of lack of drug effect for this product?

5. Were any other medication(s) or agent started with this product (concomitant medication). If yes, please provide medication's dose and start/stop dates.

6. Did the event result in an ER visit or hospitalisation? If yes, what was the duration of hospitalisation?

7. What was the next step taken since the event of lack of drug effect? (e.g. informed as a quality compliant or switched to another product, etc.)

8. Has product been taken since the event of lack of drug effect? If yes, did lack of drug effect reoccur?

9. If a consumer reports, may we contact your physician? If yes, please provide name and contact information.

Annex 5 - Protocols for Proposed and On-going Studies in RMP Part IV

Not applicable

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (If Applicable)

Not Applicable

Annex 7 – Summary of Changes to the Risk Management Plan Over Time

Not applicable, as this is the first RMP for SUBUTEX.

Annex 8 – Other Supporting Data (Including Referenced Material)

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